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OCCIPITAL AND POSTERIOR ELECTROENCEPHALOGRAPHIC RHYTHMS

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The alpha rhythm, perhaps more than any other feature of brain-wave activity, affords basic criteria for the evaluation of maturation and normality. Its occipital dominance and relation to light perception were among the earliest observations in the field of clinical electroencephalography, and in honor of its discoverer, it was named the Berger rhythm. Occipital rhythms at higher frequencies than the normal, resting alpha rhythm were produced by photic stimulation in test subjects by Adrian and Matthews as early as 1934. In 1947, Goodwin called attention to a slow alpha variant rhythm, which predominated in the occipital and adjacent posterior areas, and which he felt was the same as the electrical patterns attributed by Gibbs et al. (1937, 1938) to convulsive spells that the latter had termed "psychomotor". It was Goodwin's opinion that this "dysrhythmic" pattern was not specific and that, although it was found in a high percentage of patients with psychoneurosis and idiopathic epilepsy, it was also found in presumably normal subjects. In 1957 Gastaut et al. noted this alpha variant of Goodwin in 0.8 per cent of normal subjects and in 4 per cent of neurotics; they considered that this rhythm was characteristic of psychopathic personality trends.

Attention also has been called to other rhythms of the occipital and neighboring posterior regions. Cobb noted the relationship between 2-4 c/sec. activity, which was "bilaterally synchronous and occipital", and pathology of the epithalamic region (1945). A slow, posterior rhythm at approximately 4 c/sec. has been described by Pitot and Gastaut (1956), as well as other French workers (Nayrac and Beaussart 1956; Vallat and Lepetit 1957), which most typically occurred after head injuries, and which frequently was associated with "diencephalic" signs and symptoms. Because of the close similarity of this slow, posterior rhythm to the slow, alpha variant rhythm of Goodwin, it appears more than likely that it has been missed in the past.

Another type of slow, posterior rhythm has been noted in the EEGs of children by several workers. Y. Gastaut described this rhythm in detail in 1955 during the colloquium of Marseilles devoted to the study of EEG-Psychological Correlations (quoted by Gastaut et

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al., 1957). She wrote: "It is a matter not of a slow rhythm but of slow waves which are observed in children from the age of 6 to 14 years although they persist at times into adolescence and young adult life. These slow waves occupy the posterior half of the non-dominant hemisphere (the right in right-handed) where they intermix with the alpha rhythm and react with it to eye-opening." Y. Gastaut considers these waves as being vestiges of the posteriorly-situated delta rhythm which is seen at times in childhood and she does not look upon it as an indispensable stage in the maturation of the EEG (she observes them particularly in older children and adolescents showing personality and behaviour disorders). She warns against the mistakes in interpretation which may occur when the functional nature of these posterior slow waves is not recognised, so that they may mistakenly be taken to indicate localised parenchymatous abnormality (an epileptic focus, a tumour, post-traumatic contusion, etc. . . .).

Cobb (1957) commented upon the occurrence of these posteriorly-situated slow waves in children chiefly between the age of 4 and 8 years. Gastaut et al. (1957) confirmed their existence in very young adults since they found them in 30 per cent of a series of 309 pilots and candidates otherwise normal; from the psychological point of view they have found that these slow waves are associated with an immaturity of affect which is expressed in a particular way, namely in the aggressiveness commonly found in this group.

These posteriorly-situated slow waves did not escape the notice of certain early workers. Thus inspection of the illustrations in the monograph by Henry (1944) indicates that he had observed a number of "abnormal records from normal children", which belong in the posterior rhythms under consideration. In later studies on some of these same patients, Henry had found entirely "normal" records. Although it is by no means clear, it seems possible that some of the slow rhythms noted in the posterior temporal regions of children by Hill (1944) may belong to this same group. It would appear that Lennox (1949) was aware of posterior slow waves in children, which were not abnormal. In papers in 1949 she stated, "Originally records in which slow waves appeared predominantly or exclusively in the occipital leads were classified separately, but we are now forced to the conclusion that these electroencephalograms are normal, and we have included them in the normal group." In an earlier paper (1947) she had classified these waves as abnormal. It is also noteworthy that Walter (1953) had found occipital delta by means of his automatic analyzer in 110 normal children. On the other hand, since wave form cannot be determined by means of frequency analysis, the slow posterior rhythm of children was not recognized in the frequency analysis of Gibbs and Knott (1949). Finally, in adults, the persistance of occipital slow waves was noted as early as 1944 by Brazier and Finesinger in 1 per cent of their cases.

Another occipital rhythm within the delta frequency-range and reacting clearly to eye-opening has been described by Elston, Gordon and Cobb in young children with very frequent attacks of petit mal.

Finally we should mention the potentials evoked in the occipital region by jerky eye movements which take place when an individual explores a surface showing much contrast (Evans 1953; Gastaut et Alvim-Costa 1957). These evoked potentials were first described under the term of "occipital spikes observed during eye-opening" by Y. Gastaut in 1951, and subsequently as "lambda waves" by Evans in 1952.

Contrary to the general opinion of many electroencephalographers, the electrical activity of the occipital regions is thus far from being reduced simply to the alpha rhythm and may assume very different appearances in normal people. We shall take as examples the two records illustrated in figure 1 which come from two completely normal subjects. One of these is characterised by lambda waves which only appear on eye-opening, whereas the other one on the contrary shows posterior slow waves only on eye-closure.

Because one slow posterior rhythm of pathologic significance may be confused with the slow alpha variant of Goodwin and an-

other which is found in normally developing children may be confused with other posterior pathological rhythms, or diagnosed as focal abnormality, a review of the entire problem of alpha variants and of other posterior rhythms was undertaken.

METHODS AND MATERIALS

All of the tracings were obtained with standard technique used in the laboratory directed by Professor Gastaut where Alvar machines of 12 and 14 channels were utilized. The electrodes were placed following the *Ten-Twenty Electrode System* of the International Federation. The tracings were obtained by scalp-to-scalp (bipolar) recording, following longitudinal or transverse lines. Longitudinal derivatives, showing homologous runs that could be compared, were alone selected for study in the present survey. The most anterior electrode of each derivation was connected with grid I (which produced an upward deflection when it received a negative signal), while the positive electrode was connected with grid II. A slow paper speed of 15 mm. per sec. and mean time constant of 0.5 sec. were used in accordance with the prevailing practice in France.

The patients included in the survey were:

(1) *"Normal"* — Controls. This group consisted of 500 young Frenchmen between the ages of 19 and 22, who were selected for military service. Their intellectual and physical status had been adjudged as normal or superior.[1] Although this control group of 500 "normals" is limited in its age and sexual distribution, it nevertheless served as a useful check on those conditions that were found not to be influenced by sex or age. Thus, in the study of occipital symmetry of the alpha rhythm, in the study of the slow posterior rhythm commonly associated with pathology, which occurred about equally in all age groups, and in showing that the rhythm designated as the "slow posterior waves found predominantly in youth" also occurred in the "normals", this control group proved of distinct value.

(2) *"Abnormal"* — 8,000 patients. This group consisted of all ages and conditions as referred to the EEG Laboratories operated by Professor Gastaut and his immediate associates in the Marseille area, namely Le Laboratoire d'Electrophysiologie, Hospice de la Timone and the private clinic of Professor Gastaut in Marseille.

Records showing slow posterior rhythms, which were selected from a survey of all 8,000 "Abnormals", were carefully analyzed with respect to the frequency of the slow posterior rhythm, its amplitude (slight, moderate, or

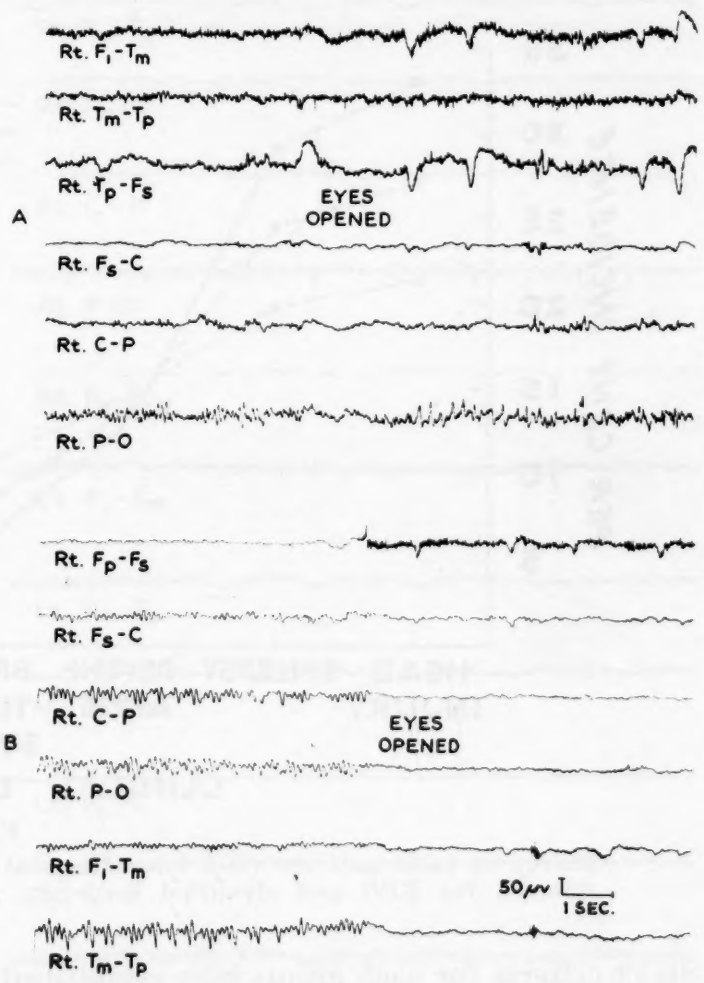

Fig. 1

This illustration shows the marked differences which may be seen in the electrical activity of the occipital regions in normals.

Records A and B represent the activity of right hemisphere in two completely normal cases; the first shows occipital lambda waves with eye-opening and the second posterior slow waves with eye-closure.

In this figure and in all the following ones we show closely-placed electrodes in longitudinal derivations, on the right hemisphere (Rt) and the left hemisphere (Lft). The electrodes are named as follows: Fp = Superior Frontal; Fi = inferior Frontal; C = Central; P = Parietal; Tm = middle Temporal; Tp = posterior Temporal; O = Occipital.

[1] These records were kindly made available to us by Dr. J. Bert and Dr. A. Roger.

great), the areas in which it appeared (topography), its symmetry and side of predominance, its form and degree of hemispheric synchronism, its pattern (continuous, occurrence in paroxysmal bursts, transient waxing and waning, or appearance as random waves), and its response to activation, including opening of the eyes, photic stimulation, and hyperventilation. In addition, the regular frequency of the occipital alpha frequency was noted in each case.

The records were classified according to the obvious groups which the survey revealed.

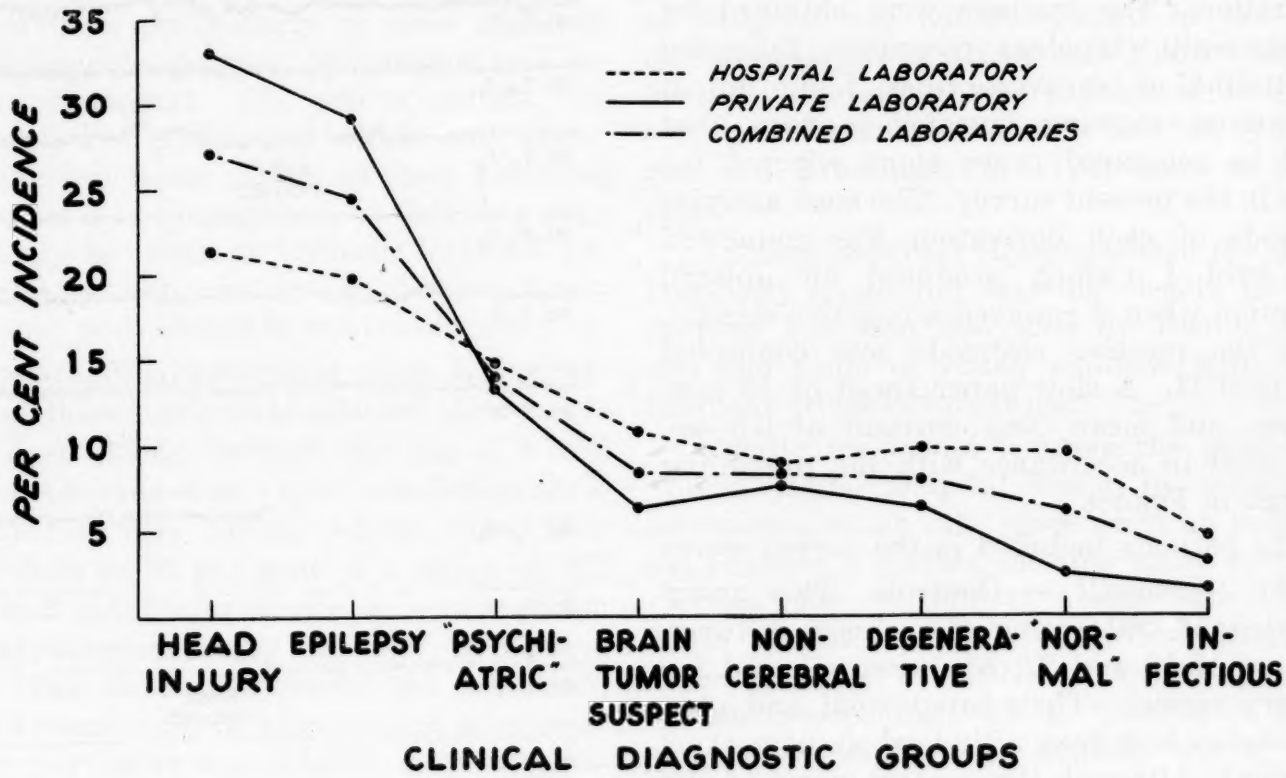

Fig. 2

Survey of 1,000 patients (500 from Hospital Laboratory and 500 from Private Laboratory) referred for EEG and classified according to clinical diagnosis.

Strict criteria for each group were established in order to obtain as pure groups as possible. Although this resulted in smaller groups than otherwise might have been obtained (and correspondingly affected the estimations of incidence), it was felt that pure groups were essential if correlations of value were to be established.

As a check upon the incidence of the smaller, pure groups which were finally established for study, a separate survey of 2,000 cases (1,000 at each laboratory) was taken in sequence. The estimates of incidence presented were based upon this repeat survey.

As a control study on normal occipital alpha, an analysis of the degree of symmetry of this rhythm, as well as its normal limits of symmetry, was made on 500 consecutive cases. The symmetry of homologous pairs of alpha waves, when recorded simultaneously, was determined on the basis of their size, duration, and form. In addition, the bilateral (hemispheric) synchronism and pattern of homologous runs of alpha waves were carefully checked. Asymmetries of size (voltages) and frequency of 20 per cent or more, which appeared with reasonable consistency, and which obviously exceeded the limits of variation that might be anticipated from the calibration of the apparatus, were considered significant.

Asymmetries of form and pattern were judged on the basis of visual scanning. The asynchronism of homologous runs recorded simultaneously was found to correspond closely, as might be expected, with consistent differences of frequency, but again could be discerned readily by visual scanning.

The clinical types and age groups referred to these laboratories are shown in survey charts in figures 2 and 6. The data shown in these charts were obtained from a review of the clinical records of 1,000 patients — 500 consecutive cases from each laboratory. In addition, a survey of the incidence of various clinical symptom complexes was made on these same groups. These surveys were obtained as an additional control in order to determine whether or not the incidence of the clinical data mentioned was different in the posterior rhythms studied from those in the general run of patients referred to the laboratories.

Material from both laboratories was used, inasmuch as the technique and personnel of each were essentially identical and the type of clinical material seen in one nicely complemented that seen in the other. Thus, at the Hospice de la Timone, a somewhat older age group was seen and correspondingly the incidence of brain tumor suspects and of degenerative conditions was higher than was true for the private clinic. In the younger age group seen in the private clinic a higher percentage of head injuries and of epilepsy was seen than was the case for the hospital laboratory.

RESULTS

In the control study on the degree of alpha symmetry, the occipital alpha was found to be essentially equal in 82.2 per cent of the cases. In 16.6 per cent of the remainder the asymmetry of potential was slight and was not associated with other types of asymmetry. In this group, the potentials predominated on the right in 12.4 per cent and on the left in 4.2 per cent. Essentially, these same percentages were found in the "normal" group of 500 selected young soldiers.

In 1.2 per cent of cases the asymmetry of potential was marked. In most of these, other asymmetries which involved form, frequency, and pattern were also observed, as well as a tendency to asynchronism. In all instances, clinical abnormalities of the patient were found which correlated with the EEG changes. It can, therefore, be concluded that marked differences of potential, if consistent, and especially if associated with homologous asynchronism, as well as asymmetries of form and frequency, probably reflect, either directly or indirectly, focal processes in or deep to the affected regions. The criteria of focal abnormality are considered in greater detail in the Discussion.

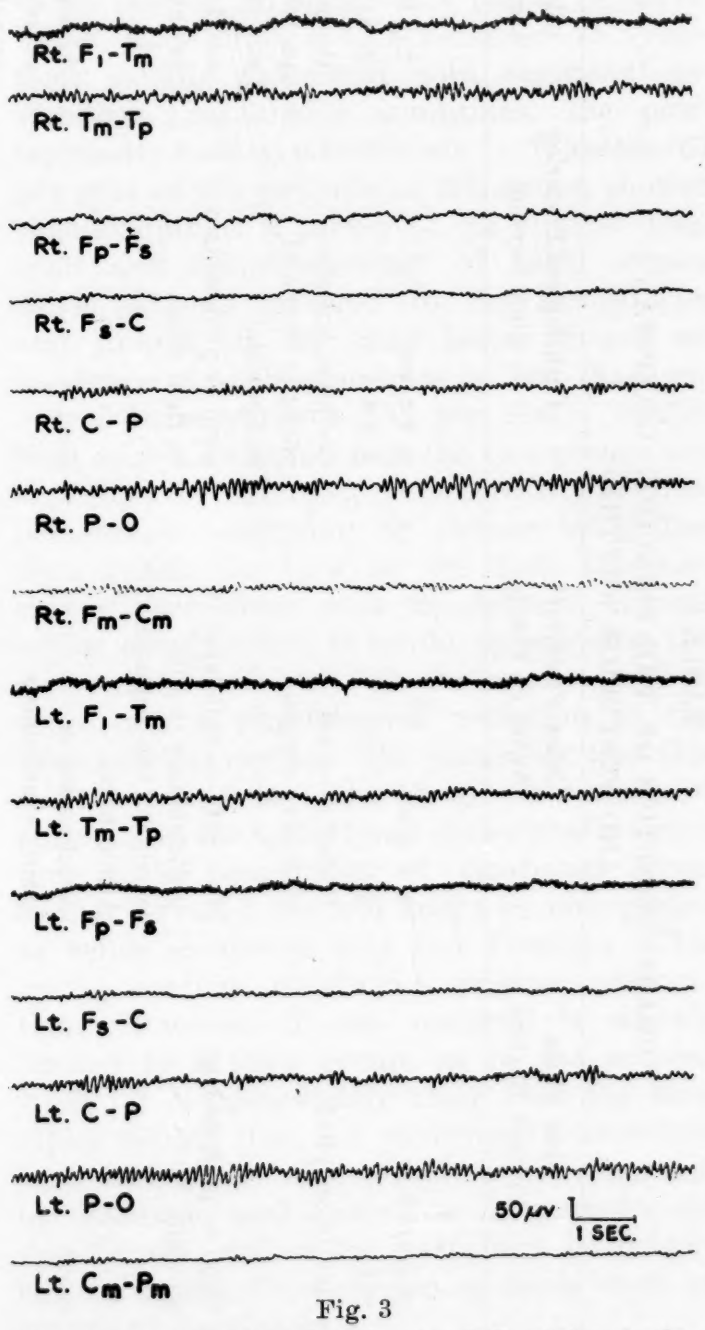

Fig. 3

Alpha variant rhythm. In this record the alpha rhythm las running precisely at 10 c/sec. and the variant rhythm at 5 c/sec. This 2 to 1 frequency ratio is as characteristic of the alpha variant rhythm as is its dicrotic form. Both are manifestations of halving ("dedoublant") of the basic alpha rhythm. The topography of the variant rhythm was slightly less extensive than that of the alpha rhythm and was observed most strikingly in the occipital and posterior temporal regions. In this instance the variant rhythm was essentially confined to the right hemisphere.

TABLE I

CHARACTERISTICS OF THE PRINCIPAL OCCIPITAL AND POSTERIOR RHYTHMS

Characteristic	Slow Alpha Variant Rhythm	Slow Posterior Waves of Youth	Pathological Posterior Slow Rhythm	Slow Posterior Rhythm Associated with Petit Mal
EEG				
Frequency	± 5 c/sec.	± 3 c/sec.	± 4 c/sec.	± 3 c/sec.
Frequency ratio	2:1	± 3:1	± 2.5:1	± 3:1
Topography	Mainly occipital	Posterior — not limited to occiput	Occipital, but also posterior temporal and parietal	Occipital, but also posterior temporal and parietal
Symmetry	Good or predominant on right	Fair only — unilateral predominance in 50% on right (non-dominant hemisphere)	Good or predominant on right side	Good with bursts, otherwise asymmetrical in 50%
Synchronism	Good	Synchronous or poorly synchronous	Good	Synchronous with bursts, otherwise chiefly asynchronous
Form	Dicrotic	Polyrhythmic — random	Sinusoidal, small amplitude	Sinusoidal, high amplitude
Pattern	Bursts — 3 out of 4	Bursts — rare Continuous (wax and wane) — Very rare	Bursts (longs) — 2 out of 3	Bursts (briefs) — very frequent Background — continuous (wax and wane) — rare
	Continuous — 1 out of 4	Sporadic — frequent	Continuous — 1 out of 3	
RESPONSE TO ACTIVATION				
Opening of eyes	Strong blocking	Strong blocking	Strong blocking	Strong blocking
Hyperventilation	No effect or usually accentuated	No effect or accentuated	No effect or usually accentuated	Accentuated and usually causes bursts and episodes of W. & S.
Photic stimulation	Usually blocks, and driving effect	Usually no effect	Usually blocks	Usually no effect, but may activate
CLINICAL				
Age group	20-60 years	Chiefly 5-25 years	All ages	Chiefly children
Trauma	1 out of 6	1 out of 6	2 out of 3	Rare
Spells	Almost none	1 out of 3	1 out of 3	100% (petit mal)

Four occipital groups of rhythms or wave types have been identified and analyzed in significant numbers of cases. Still other posterior rhythms were observed in 1.1 per cent of cases, but these were either atypical variants of the rhythms considered, or for any particular type appeared in such limited numbers as to preclude a correlative analysis.

(1) *Slow Alpha Variant Rhythm.*

The slow alpha variant rhythm as observed in its pure form in the group of records selected for the purpose of the present study was found to have a frequency of 4 or 5 c/sec. and a two-to-one relationship to the basic alpha frequency of the same patient. This rhythm occurred mainly in the occipital regions, was essentially symmetrical or in some patients predominated on the right and showed bilateral, hemispheric synchrony. Its form was typically dicrotic and in pattern it usually appeared transiently in a paroxysmal fashion. This rhythm showed strong blocking to opening of the eyes and also as a rule to photic stimulation, being frequently replaced in the latter instance by a driving effect. Hyperventilation either did not modify the slow alpha variant rhythm or more usually served to accentuate it. These characteristics have been tabulated and are shown in comparison with the features of other posterior rhythms in table I. The dicrotic form and clear doubling of the basic alpha rhythm is illustrated in figure 3.

Distinct runs of the slow alpha variant rhythm were found in slightly less than one per cent of our "abnormal" records. Only one case of slow alpha variant rhythm was found in the control group of 500 "normal" subjects. Although this incidence is well below that observed by Goodwin (1947), the selection of alpha variant cases for the purposes of this study was strictly limited to those showing a dicrotic form and with a frequency rate that was clearly related to the basic alpha rhythm of the same patient. As will be noted in more detail in the Discussion, our study has emphasized the necessity of making a differentiation between the primary rhythms of the cortex and their replacement by rhythms of presumable diencephalic or brain stem origin. In the report of Goodwin (1947), it is clear that atypical alpha patterns, as well as distinct dysrhythmias and also probably the other rhythms considered in the present paper, were included as examples of slow alpha variants.

The clinical data on this group of patients showed no significant points of correlation, aside from a high incidence of symptoms usually associated with emotional instability (psychiatric conditions, the posttraumatic head syndrome, etc.). Whereas, 61 per cent of the patients in this group showed such symptoms, a survey of the clinical diagnosis and symptomatology of 1,000 consecutive patients referred to the laboratories and judged on the same basis, showed an incidence of such symptoms in less than one out of three patients (30 per cent). Statistical analysis showed that the two groups are significantly different, the probability of these percentages occurring by chance being less than 0.001. In view of the fact, however, that a correlation with no definite clinical entity was possible, it would appear that the slow alpha variant, as its name implies, represents a physiological variation of the basic cortical rhythm. The possibility that this variation may be induced by alterations of function in the underlying diencephalic structure under conditions of emotional stress cannot be ruled out and might be interpreted as being consistent with our findings. This would confirm Goodwin's original observation. However, if case material is strictly limited to a pure group, as in the present study, it is immediately clear that the slow alpha variant does not significantly correlate with convulsive susceptibility, as suggested by Goodwin, and again has no pathological significance, unless the pathology be deeply located in the diencephalon or brain stem as suggested previously.

(2) *Slow, Posterior Waves Found Predominantly in Youth.*

In spite of considerable variability the slow posterior waves found predominantly in youth showed distinctive features and in their pure form can readily be recognized by an experienced electroencephalographer. The

amplitude of these waves tended to be great and in general they stood out strongly against the otherwise normal background of occipital alpha. This wave type assumed a polyrhythmic form. Frequently three or four alpha were superimposed upon the positive phase of one slow wave and this at times gave the impression of an extra slow variant, formed as a result of tripling or even quadrupling of the basic alpha frequency. Sequences of sinusoidal waves associated with high-voltage sharp waves of negative potential (see fig. 4) constituted a common pattern. Random slow waves of sinusoidal or irregular form were frequently interposed with sequences of the types previously described, or again occurred alone. Aside from random slow waves, the pattern sometimes consisted of long runs of the wave types mentioned or appeared in an almost continuous fashion with some waxing and waning. The slow posterior waves found predominantly in youth usually blocked to opening of the eyes. Although, as a rule no alteration occurred with photic stimulation, in some cases these slow posterior waves were accentuated, or only appeared with photic stimulation. Hyperventilation often accentuated this wave type.

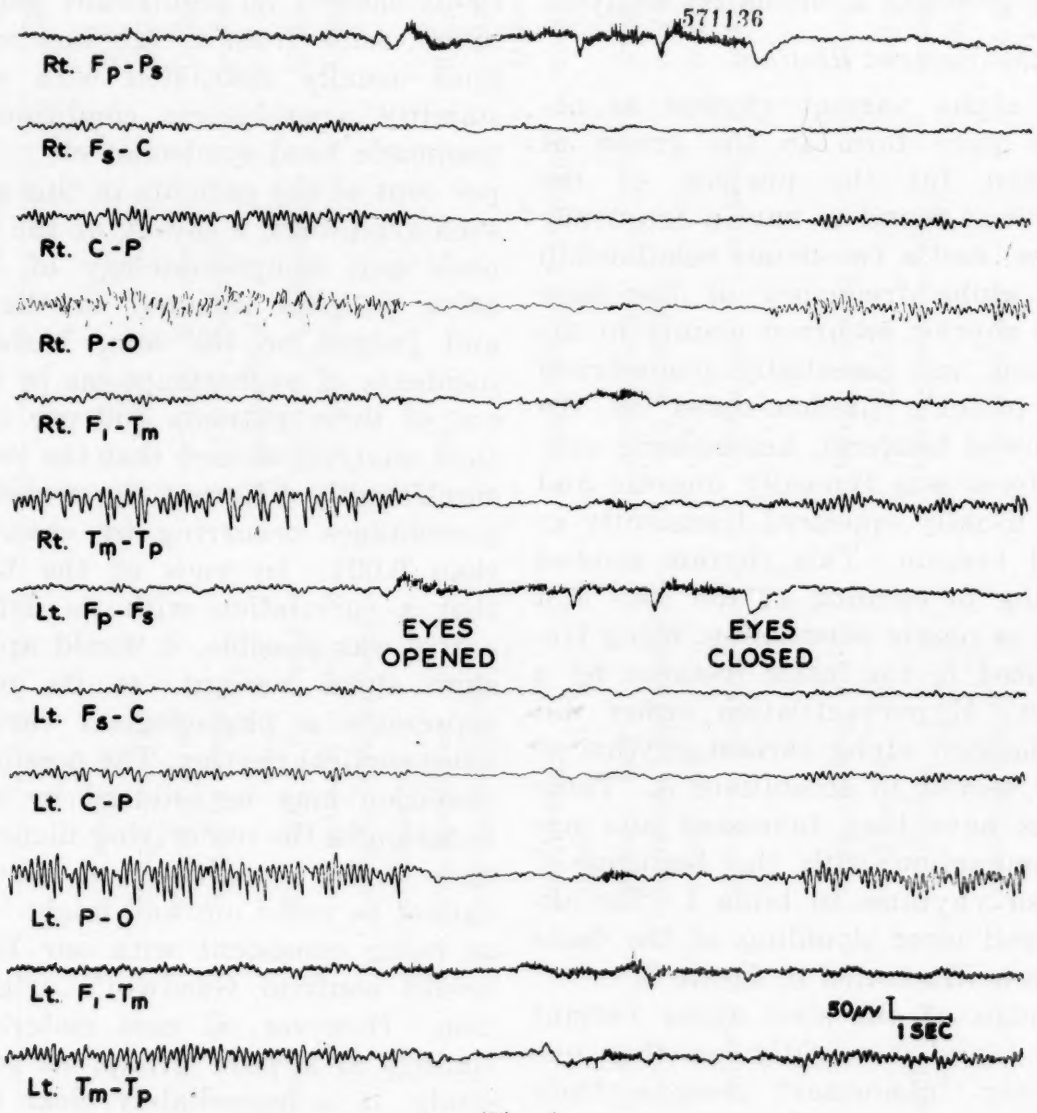

Fig. 4

Illustration of the slow posterior waves found predominantly in youth, which "block" at the same time as the alpha rhythm on opening of the eyes. The other principal characteristics of this wave form that are illustrated in the figure are as follows: a topography which is less extensive than the alpha rhythm and which is most striking in the occipital, posterior temporal, and parietal regions; a predominance in the right hemisphere; and the superimposition of alpha waves on the slow posterior waves.

Because of the random and variable appearance of this wave form, the term "rhythm" has not been applied to it. Likewise, it is difficult to assign it a definite frequency. The usual duration of the waves varied from 0.25 to 0.35 seconds, so that, when a series of waves did appear in succession, a frequency rate of 3-4 c/sec. was typical. Correspondingly, parietal areas. It was asymmetrical in approximately 50 per cent of the records, and when asymmetrical it usually showed a predominance on the right side. In several instances of left sided predominance, it was of interest to us that the patients were left handed. This relationship, however, should be studied further since some exceptions to a

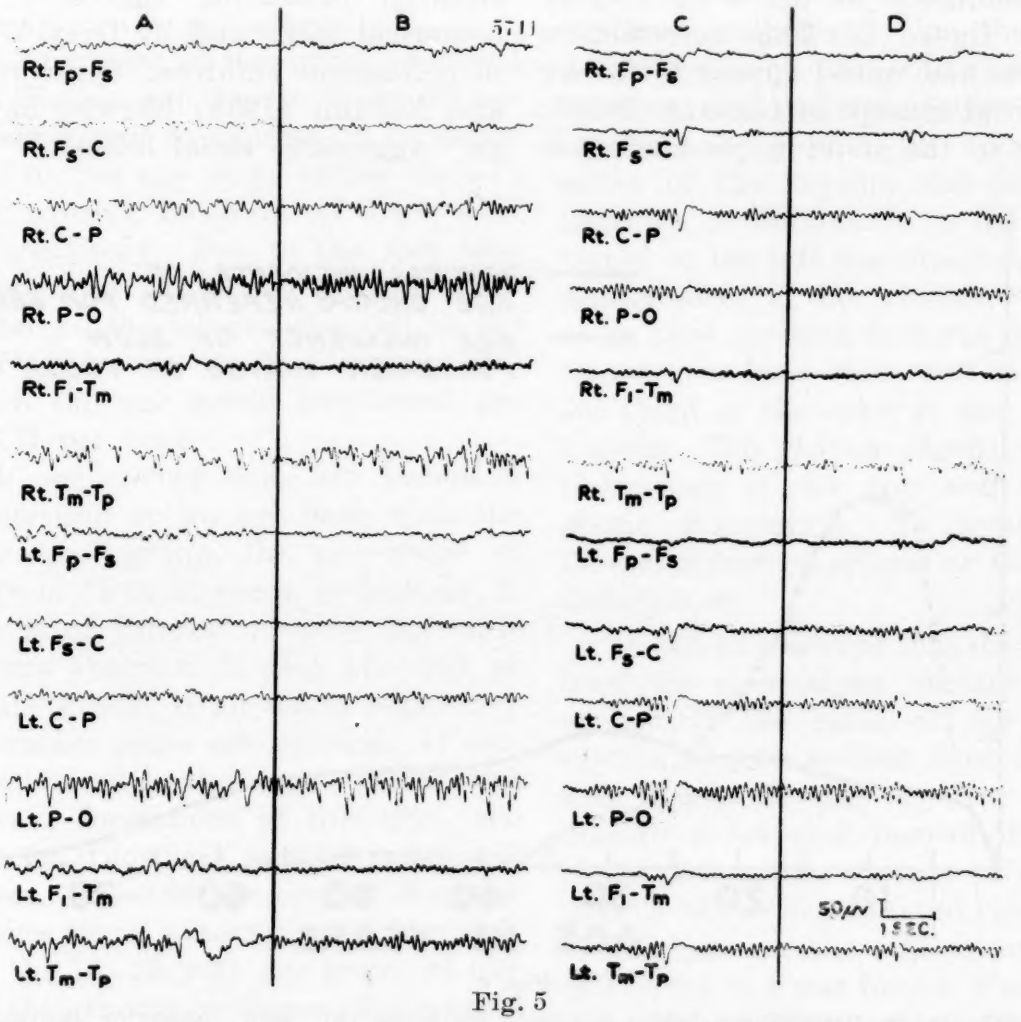

Fig. 5

Examples of the slow posterior waves found predominantly in youth, which appeared in a pseudo-rhythmical pattern (2 - 3 c/sec.) in one patient illustrated in A and B and sporadically in another patient illustrated in C and D. In A and C the slow positive element of the wave was directly preceded or followed by an alpha wave, the in-phase combination of which produced the appearance of spikes. In B and D a more rapid negative phase predominated to produce a similar "spiky" form. The illustrations are from two patients of 15 and 16 years of age respectively, who were known to be normal and who, in fact, were superior in their intelligence and behavior. In both instances the slow posterior waves were bilateral and predominated on the right.

the relationship of this wave type to the regular frequency of the occipital alpha rhythm in the same patient approximated a 3-to-1 ratio. Although it predominated in the occipital regions in most cases, it was by no means confined to these areas and frequently appeared also in the posterior temporal and relationship with the non-dominant hemisphere were found. When essentially symmetrical, the waves of the two sides tended to be synchronous. However, asynchronism appeared when this wave type was strongly asymmetrical.

The main characteristics of the slow pos-

terior waves found predominantly in youth are presented in table I and typical examples are shown in figures 4 and 5.

An over-all incidence of 6 per cent was found in the survey of our ''abnormal'' group.

Two points were emphasized by the clinical study of this group. The age groups principally involved were distinctive with a striking predominance in the 6 to 25-year groups, as in figure 6. This corroborates previous reports and would appear to favour the developmental concept of Gastaut (1956). Corresponding to the striking predominance that it was not associated with any particular clinical entity or symptom complex, other than ''immaturity'' and has been found in ''normal'' subjects.

It would appear that the slow posterior waves found predominantly in youth are in essence the same as the delta and theta rhythms described by Denis Hill (1944) in children presenting aggressive, schizoid or hysterical traits and by Grey Walter (1953) in delinquent children. Quite recently Cohn and Nardini (1958) likewise have associated an ''aggressive social behavior'' with a ''bi-

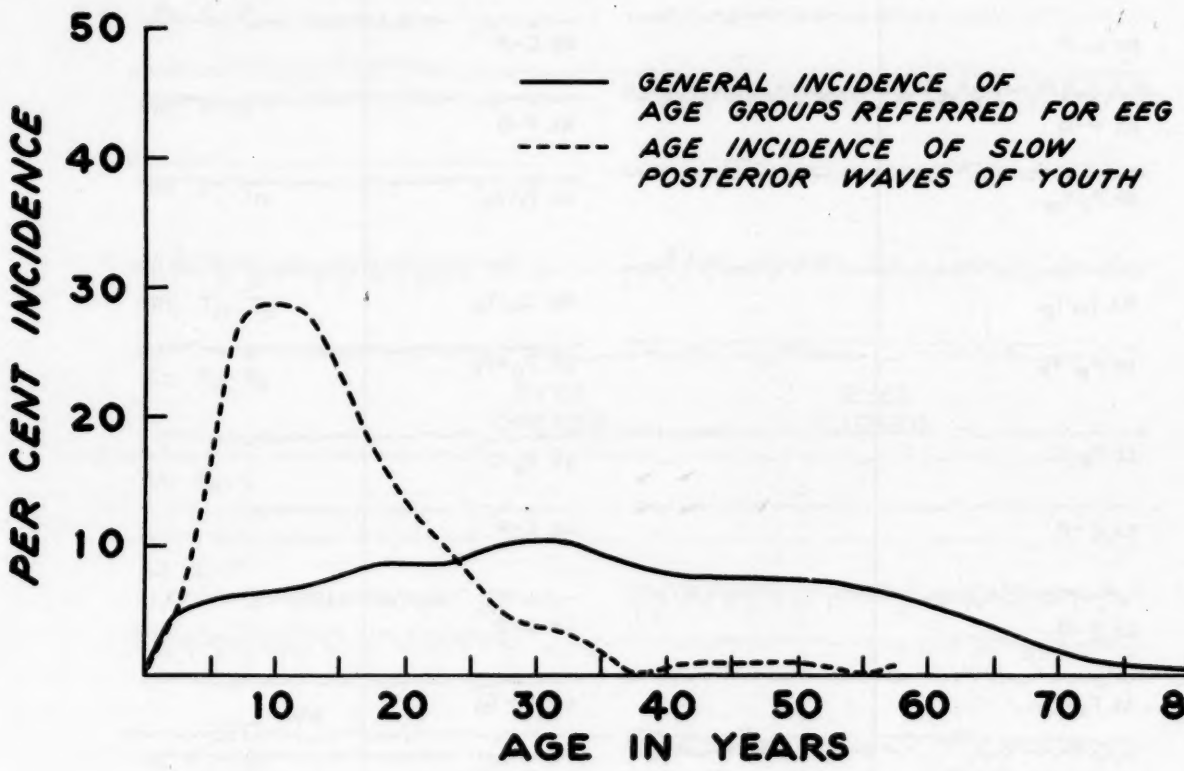

Fig. 6

Comparison on a percentage basis of age incidence of slow posterior waves found predominantly in youth and the general incidence of age groups referred for EEG.

of these posterior slow waves in youth, symptoms of the type usually associated with ''immaturity'' were commonly noted in the older patients exhibiting this electroencephalographic pattern. It is of some interest in this connection that Hill (1952) observed the development of posterior temporal slow wave foci in children which later on disappeared and which he related, along with other changes, to defects of maturation. The developmental concept of this wave type is further strengthened by the second factor emerging from the clinical survey, namely, lateral occipital slow activity'', which undoubtedly corresponds to this same slow posterior wave group. Clinical correlations between this graphic element and behavioral traits were reported at the symposium of Marseille in 1955 by Gastaut et al. (1956) who found a connection between the presence of slow posterior waves and an affective immaturity. A further correlative study is at present being made in the laboratory at Marseille between the slow posterior waves found in 500 normal subjects, 20 years of age, and 55 psychological variants concerned with dif-

ferent behavioral traits. In this study in which the statistical significance was precisely calculated by means of an electrical calculator, it would appear that no valid correlation has been found between the presence of slow posterior waves and personality characteristics, such as aggressiveness and impulsiveness. Because this study was underway at the time the present study was completed, a correlation of this type was not attempted.

Since 85.3 per cent of this group occurred in the 6 to 25-year age group, it would appear more significant to express its incidence with respect to this age range rather than in terms of the over-all incidence of 6 per cent mentioned previously. Due to the fact that less than 30 per cent of the general run of patients referred to the laboratories fell in the 6 to 25-year age range, the incidence of this wave type in the age group mentioned approximated 17 per cent.

Although our survey does not permit a precise comparison on an age basis with the "normal" control group, the age range of which was from 19 to 22 years, inclusively, it nevertheless is of interest to note that this wave type was observed in 18.4 per cent of this "normal" group, if all waves suggestive of this pattern are taken into account. If consideration is limited to the more distinct and definitive wave formations of this type, the incidence in the "normal" control group fell to 10 per cent. Since 28 per cent of the slow posterior waves found predominantly in youth occurred in the 16 - 25 year age group of our survey, and the general incidence of this same age group was 17 per cent, the incidence of this wave type in the age group mentioned was 9.9 per cent, a figure which compares very closely with the incidence in the more rigidly selected "normal" control group. A comparable incidence of this wave type in "normals" would appear to favor its normal developmental significance and argue against any connotation of abnormality.

(3) *Slow Posterior Rhythm Commonly Associated with Pathology.*

The characteristics of the posterior slow rhythm, which in many respects simulates the slow alpha variant, but which frequently has been found to have pathological significance (Pitot and Gastaut 1956; Nayrac and Beaussart 1956; Vallat and Lepetit 1957), is shown in table I. An example of this rhythm is shown in figure 7. This rhythm was found in one per cent of our "abnormal" records and in only 0.20 per cent of our control group of 500 "normals".

This slow, posterior rhythm, like the other rhythms considered in this study, predominated in the occipital areas, but posterior temporal and parietal regions were commonly involved along with the occiput. The symmetry of the rhythm was usually good, although a predominance on the right and more rarely on the left was observed. The bilateral synchronism of the rhythm was good. One of its most striking features was its tendency to occur in long runs, and in approximately one third of the cases it was essentially continuous. This rhythm showed strong blocking to opening of the eyes and also usually to photic stimulation. To hyperventilation it showed either no effects or more usually was accentuated.

It will be observed that this rhythm differs from the slow alpha variant in several respects. If the ratio of the regular alpha rhythm of each patient is carefully measured with respect to this rhythm, a 2.5-to-1 relationship is revealed, instead of the 2-to-1 ratio of the slow alpha variant. Furthermore, the ratio is not a well defined one as in the case of the alpha variant, since a range of variation of 2 ± 0.5 to 1 was found. Possibly reflecting this lack of a relationship to the regular alpha frequency in still another respect was the difference of form. A more pure sinusoidal wave form was usual in this group instead of the dicrotic form of the slow alpha variant.

The clinical study of this group of patients revealed two main points of correlative significance: (1) a high incidence of head trauma; and (2) a high incidence of symptoms suggestive of emotional instability. The 62 per cent incidence of head trauma in this group may be seen to be significantly higher than the incidence of this factor in the general run of patients referred to the laboratory (27 per cent). Statistical analysis showed

that these two groups were significantly different, the probability that these results might occur by chance being less than 0.001. Corresponding to the incidence of head trauma, it was not surprising to find that such symptoms as headache, vertigo, and easy fatigue had a significantly high incidence, as compared with the incidence of such symptoms in the general run of patients who were referred to the laboratories. Nevertheless, a surprisingly high incidence of similar symptoms, usually associated with emotional instability, was found in the patients of this group. Including the post-traumatic head syndrome cases, such symptoms were found in 3 out of 5 patients (60 per cent), whereas in the general run of patients, such symptoms occurred in less than one out of three patients (30 per cent). Statistical analysis showed these two groups to be significantly different, the probability that the results indicated might occur by chance being less than 0.001. It would appear, therefore, that the possibility of emotional symptomatology in association with a dysfunction of the diencephalon, much as discussed in the preceding section on the slow alpha variant, must be kept in mind. This was further suggested by the relatively high incidence of other diencephalic signs and symptoms (abnormalities of development, disturbance of menstruation, and other evidence of endocrine dysfunction of possible

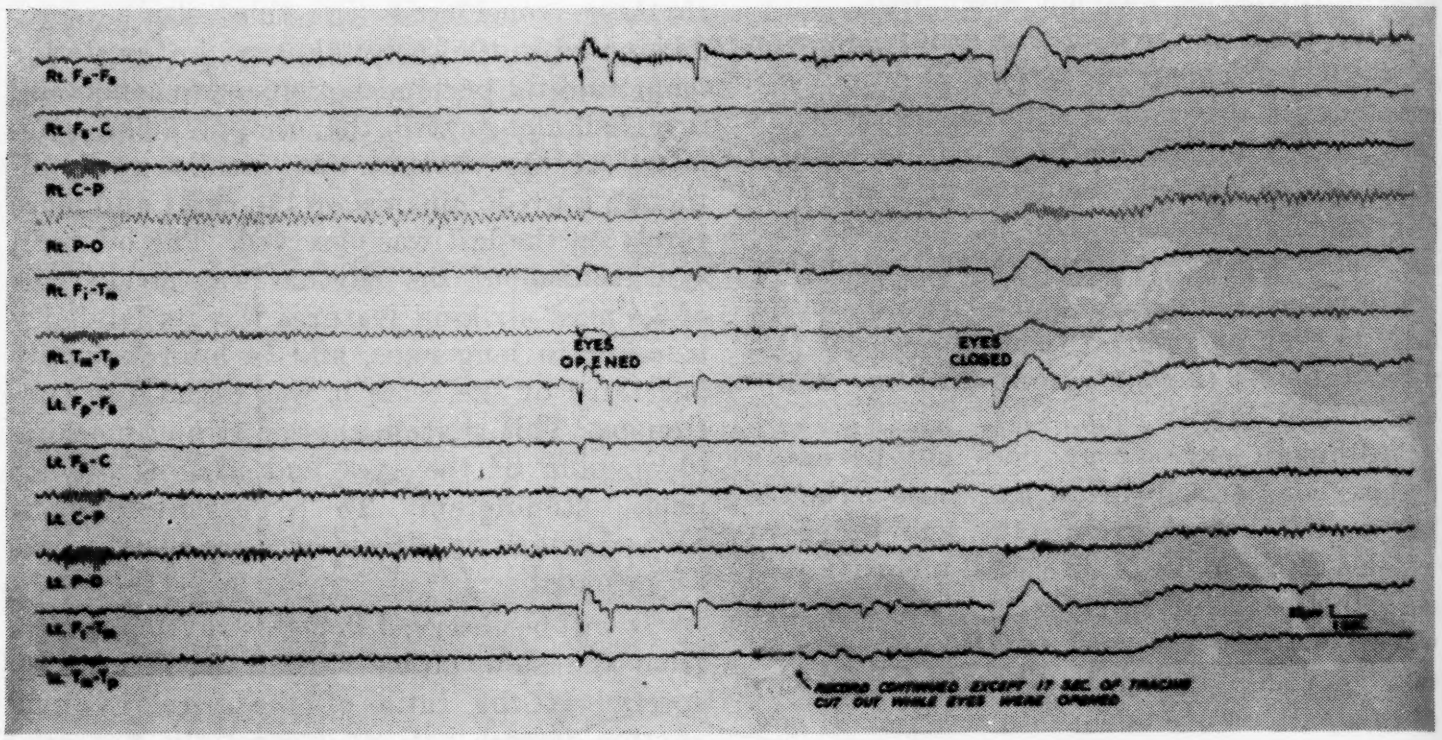

Fig. 7

Illustration of the slow posterior rhythm commonly associated with pathology. The patient was a 30-year-old female nurse who four years before had sustained a serious head injury associated with unconsciousness. However, she had been able to work the following day and since. In the next month her normal menstrual period failed to develop and she had not menstruated since the injury. Because her urinary excretion of pituitary gonadotropin was normal, it was felt that her amenorrhea was not on a pituitary basis. Examination and cyto-hormonal biopsy of the endometrium had shown an oestrogenic deficiency.

The usual characteristics of this slow posterior rhythm are explained in the text. Note the short burst of alpha which preceded the reappearance of the slow waves on closing of the eyes. Also note the slowing of the posterior rhythm (from 4 - 5 c/sec. to 3.5 c/sec.) as the amplitude was augmented. A shifting frequency rate in this range was found to be typical of this rhythm which, therefore, bears no specific relationship to the frequency rate of the underlying alpha rhythm.

hypothalamic origin, which were found in approximately one of three patients of this group).

Also, as is discussed later at greater length (see Discussion), the slow rhythm of this group, which involved both occipital regions essentially symmetrically and synchronously, would appear to have a deep central origin from either the diencephalon or brain stem. This would be in keeping with the points made previously with respect to the frequency and rhythm has also been termed by Pitot and Gastaut, would not appear to be a good name either, since nearly one half of the cases did not show a 4 c/sec. rhythm, and other posterior rhythms may assume this frequency.

Only one other clinical factor appeared to be of significance in this group. Whereas the slow alpha variant was found chiefly in an older age group (from 20 to 60), all ages were represented in the slow posterior rhythm commonly associated with pathology.

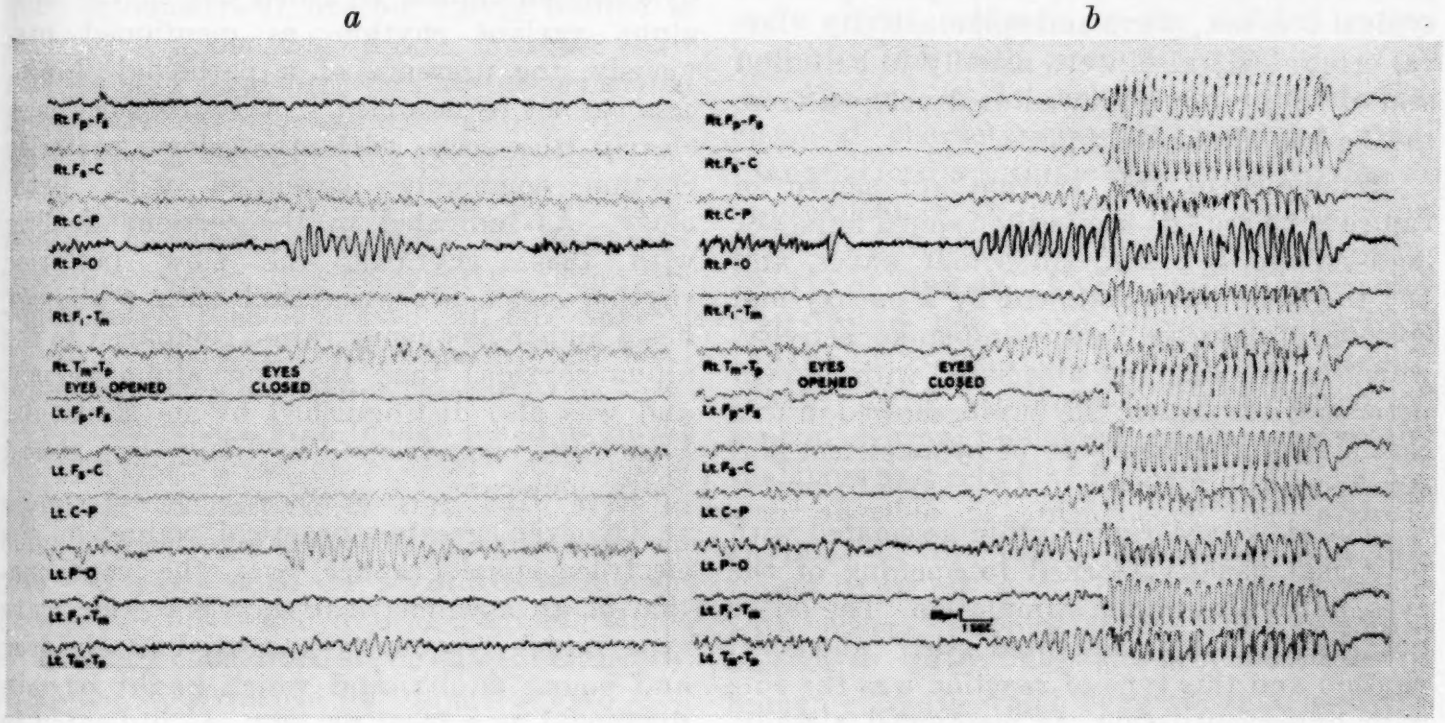

Fig. 8

Examples of the slow posterior waves associated with petit mal from two different patients of the same age (12 years). Note the close similarity of the bursts of slow, sinusoidal waves at 3 c/sec. in the posterior temporal and occipital regions of both sides. The parietal areas were involved only slightly. In both cases the episodes were accentuated by closing of the eyes. In one instance this was followed directly by a discharge of wave-and-spike activity typical of petit mal. The characteristics of the slow posterior waves associated with petit mal are sufficiently precise as to be of considerable diagnostic help, even though not showing the 3 c/sec., wave-and-spike pattern typical of petit mal. They often appear alone, as shown in the first example, or may occur before such typical bursts, and again sometimes last after the more specific discharge has disappeared.

form of this rhythm, namely, that it is fundamentally different from the normal alpha rhythm of the cortex. Because of its frequent pathological significance, the term "slow posterior rhythm commonly associated with pathology" would seem to be a better designation for this rhythm than the term "slow alpha rhythm" sometimes used in France by those who first noted this rhythm. The "4 c/sec. posterior rhythm", as this

4) *Slow Posterior Rhythm Associated with Petit Mal.*

The slow posterior rhythm associated with petit mal is entirely different from the slow posterior rhythm commonly associated with pathology just described. In general it is slower, of greater amplitude, and appears in shorter bursts. The difference in pattern is sufficiently striking to preclude any possible confusion with either the slow posterior

rhythm commonly associated with pathology or again with the other slow posterior rhythms previously considered. Since the other rhythms considered did frequently occur at 3 c/sec., it also should be clear that not all children showing 3 c/sec. activity posteriorly have petit mal.

Table I shows the distinctive features of this rhythm to be paroxysmal bursts of high voltage, 3 c/sec., sinusoidal waves in the occipital and adjacent areas. Short paroxysms of typical 3 c/sec., wave-and-spike activity (larval or clinical) also, were usually to be found and often directly followed or developed from the 3 c/sec. sinusoidal bursts.

Examples of this rhythm are shown in figure 8, where (*a*) shows the typical bursts of high-voltage, 3 c/sec., sinusoidal waves, and (*b*) the same burst followed by a paroxysmal episode of 3 c/sec., wave-and-spike activity, which in this case was associated with clinical petit mal. As shown, the bursts showed in this case a strong tendency to be symmetrical and synchronous.

The slow posterior rhythm associated with petit mal usually blocked to opening of the eyes, but not to photic stimulation. The latter not infrequently activated this abnormal rhythm and this type of reaction was the rule with hyperventilation, as mentioned already. This rhythm showed an incidence of only 0.5 per cent in the survey of our "abnormal" group. As a point of curiosity, although none of the 500 "normal" controls showed this rhythm in their resting wake records, it appeared in two subjects with activation, in one with hyperventilation and in the second with photic stimulation.

Aside from the clinical association of this rhythm with petit mal and an incidence in a younger age group, as might be expected, no other correlative factors of significance were found.

In 100 EEG tracings obtained on 36 patients with clinical petit mal, the bursts of 3 c/sec. activity were noted to occur occipitally or posteriorly in 39 records on 23 of the patients of this group. The incidence of posterior bursts thus was 61 per cent of 64 records obtained on the 64 per cent of patients showing such activity.

DISCUSSION

The occasional occurrence of a slow posterior rhythm, which could be distinguished from slow alpha variant, and which was associated with abnormality (especially head trauma) in a high percentage of cases, was of particular interest. Although diencephalic dysfunction cannot be ruled out in the slow alpha variant rhythm, as mentioned previously, the presence of a pathological process cannot be assumed in this instance as is clearly the case with the slow posterior rhythm commonly associated with pathology. As indicated in the sections dealing with these rhythms, the slow posterior rhythm commonly associated with pathology has a higher frequency ratio (compared to the alpha rhythm) than the slow alpha variant and was also distinguished by its sinusoidal form and occurrence in long or almost continuous runs.

Of even greater practical value to the electroencephalographer, was the confirmation of an asymmetrical slow posterior wave type, which frequently appeared in children and young adults, and which might be misdiagnosed as a focal process. As indicated in table I, the slow posterior waves found predominantly in youth possess many of the features of an electroencephalographic focus. Indeed, when this wave pattern appears in an exaggerated form and assumes some of the usual characteristics of an EEG focus, differentiation may be difficult or impossible.

The first and essential feature of a focus is that some abnormality of rhythm be consistently localized from a topographical standpoint. A striking asymmetry of the rhythm as found in the homologous areas involved in an obvious counterpart of such a focal process. Differences of potential, wave form, frequency rate, and alterations of hemispheric synchronism constitute the component elements characterizing homologous asymmetry. Focal dysrhythmias also tend to persist

in a continuous fashion and, as a rule, do not alter appreciably with opening of the eyes or photic stimulation.

Although the slow posterior waves found predominantly in youth may simulate any one of these characteristics, it is unusual for this wave type to assume more than one or two of the focal characteristics mentioned. A close scrutiny of the records, for example, will show that the slow posterior waves found predominantly in youth, although frequently quite asymmetrical, are but rarely limited to one area or to one side. Again, the other characteristics of focal processes are not exhibited in a sufficiently consistent fashion by this wave type to warrant a focal diagnosis.

In spite of the differential points mentioned, borderline examples of the slow posterior waves predominantly found in youth have been observed in our survey, which are difficult to distinguish from focal processes. Such borderline cases must be viewed with suspicion, even though noted in one of the posterior areas of a child. A strongly asymmetrical pattern of this wave type in older subjects (and especially those over 25 years of age) must be regarded with even greater suspicion and a focal diagnosis might be seriously considered if the subject clinically exhibited no evidence of "immaturity."

In the records of the slow posterior waves found predominantly in youth which show a bilateral and more symmetrical pattern, this wave form might also be confused with other slow posterior rhythms related to abnormalities of the diencephalon or brain stem. As noted under the slow posterior rhythm commonly associated with pathology, head injuries presumably associated with cerebral concussion are a common cause of such dysfunction. Meningo-encephalitic conditions (especially tuberculous) and space-consuming processes may also produce similar posterior rhythms, which have been recognised by others in the past (Cobb, 1957; Faure *et al.*, 1951).

The practical importance of the proper recognition of the slow posterior waves predominantly found in youth is obvious and need not be stressed further, except to point out that in addition to the fact that these waves do not signify a focal process, they likewise are devoid of any special connotation of convulsive susceptibility.

Aside from these practical, diagnostic considerations, the slow, posterior rhythms and wave types considered in this study are of great interest from the standpoint of their physiological origin. Although thalamocortical reverberating circuits were formerly postulated as the basis of the alpha rhythm, more recent evidence on the isolated cortex indicates that such circuits are not essential. As Eccles (1953) has noted, the electrochemical characteristics of neuronal membranes afford a suitable basis for a rhythm of approximately 10 c/sec. The experimental studies of Morison and Dempsey (1941, 1942, 1943), of Jasper (1949, 1957; Jasper and Van Buren 1953) and Droogleever-Fortuyn (1947, 1953), and of Moruzzi and Magoun (1949) have established the presence of central neurophysiological mechanisms in the thalamus and reticular formation of the brain stem capable of influencing the intrinsic rhythms of the cortex bilaterally and diffusely. One of us (Aird) in collaboration with others (Ogden *et al.* 1956; Garoutte and Aird 1958) has adduced evidence in human subjects which suggests that both the normal and abnormal rhythms of the brain possess a high degree of homologous synchrony (except for the asynchrony to be found directly over areas of focal pathology) which could best be explained in terms of a central, regulating "pacemaker" mechanism utilizing the diffuse and bilateral projection systems suggested by the experimental studies to which reference has been made. From this standpoint the normal alpha rhythm may be considered to consist of the intrinsic rhythms of the cortex, synchronized by the "driving" effect of the central "pacemaker" mechanism. In the infant and young such cortical rhythms would be poorly established and poorly regulated. Depending presumably upon differences of maturation, slower rhythms of the type designated as "the slow posterior waves found predominantly in youth" might

be found. As the process of maturation advanced, this type of rhythm could be found only occasionally and in older patients would presumably constitute evidence of a failure of proper maturation or at least evidence that the normal physiological accompaniments of maturation had not developed. The age survey for this group would appear consistent with such an interpretation. The relative absence of this rhythm in the age group under five might be explained in terms of its being obscured by the gross slow wave activity characteristic of infancy. Our present lack of knowledge of both the intrinsic cortical rhythms of youth and of the developmental stages of the ''pacemaker'' mechanism preclude discussion to advantage beyond the general point already considered. It is of some interest, nevertheless, to conjecture upon the possibility that the slow posterior waves found predominantly in youth are compounded of multiple alpha waves, as already suggested, but show local differences that reflect the various stages of local maturation, as well as differences of regulation on the two sides by the ''pacemaker'' mechanism.

Evidence was also adduced (Ogden, Aird and Garoutte 1955, 1956) which suggested that the pathophysiologic influence of gross, focal lesions might influence the ''pacemaker'' mechanism to produce the synchronous, generalized dysrhythmias so frequently associated with such focal processes. That pathological processes may be associated with diffuse and synchronous dysrhythmias of presumably diencephalic origin, however, is most strikingly seen in petit mal variant cases. The diencephalic origin of the slow, posterior rhythm associated with petit mal would also seem clear. The 3 c/sec. activity of this rhythm, which appeared paroxysmally and in a synchronous fashion in the posterior cortical regions of both sides, obviously blended with and gave every appearance of being an integral part of the 3 c/sec. wave-and-spike activity. That such a mechanism might produce the slow, posterior waves considered in this study seems entirely plausible and in the case of the slow posterior rhythm commonly associated with pathology would be in keeping with both the topography found in the slow, posterior rhythm associated with petit mal and the concept suggested above, whereby diffuse and bilaterally synchronous dysrhythmias may be produced as a result of pathophysiological influences acting upon a central ''pacemaker''.

The clinical data of the patients in whom the slow posterior rhythm commonly associated with pathology was found would seem to substantiate this latter point, inasmuch as head trauma is known to be associated with diencephalic and brain stem pathology in a high percentage of cases and the symptoms elicited from many of the non-traumatic cases of this group were also suggestive of a pathophysiological involvement of these same deep regions.

An analogous study of the 3 c/sec. occipital delta activity of patients with petit mal and a similar posterior slow rhythm found in patients with brain stem or thalamic lesions by Elston, Gordon and Cobb (1956) who concluded that both rhythms were of ''centrencephalic'' origin. Although consistent with our own findings and concept, it should be pointed out that the thesis postulated in the present study goes well beyond the English study in suggesting a pacemaker mechanism in explanation of the synchronous activity found in these as well as in other conditions associated with a slow rhythms of the occiput and adjacent posterior regions of both cerebral hemispheres. The importance of the pacemaker concept as pointed out in other studies (Aird and Garoutte 1958), lies in the fact that this mechanism can be disturbed by the pathophysiological activity of lesions not necessarily situated themselves in the deep pacemaker mechanism or structures.

CONCLUSIONS

1. The incidence, characteristics and clinical correlates of slow posterior rhythms were studied in the electroencephalographic records of 8,000 ''abnormal'' patients and 500 ''normals''. Four rhythms or wave types were identified in sufficient numbers to permit analysis. Strict criteria were established for each type in order to obtain pure groups for purposes of clinical correlation.

2. A slow alpha variant rhythm which showed a two to one frequency relationship to the underlying occipital alpha rhythm was found in slightly less than 1 per cent of the "abnormal" records and in 0.2 per cent of the "normals". Since no correlation could be established between the pure variant rhythm and any clinical entity, it was concluded that the slow alpha variant, as its name implies, probably represents a physiological variation of the basic cortical rhythm. Symptoms usually associated with emotional instability were found in over half of the patients in this group. This suggestive correlation with a symptom complex confirms Goodwin's original observation on this point and raises the question of a dysfunction, presumably in the diencephalon, or other deep structures. No correlation with convulsive susceptibility could be established.

3. Slow posterior waves at 3 to 4 c/sec., which were asymmetrical in 50 per cent of the cases, and which were characterized by a polyrhythmic and "spiky" form or again appeared as random slow waves, were found in 17 per cent of the "abnormal" group between the ages of 6 and 25 years, in 9.9 per cent of the "abnormal" group between the ages of 16 and 25 years, and in 10 per cent of the "normal" group between the ages of 19 and 22 years. Although the term "rhythm" cannot justifiably be applied to this group, it nevertheless showed distinctive features which make it a recognizable EEG entity. Approximately 85 per cent of the waves of this type were found in patients between the ages of 6 and 25 years. Since this wave type showed no correlation with any particular clinical entity in the "abnormal" group and was found with equal incidence in "normal", it was concluded that it probably reflected variations of normal maturation and development. For this reason it has been termed "slow posterior waves found predominantly in youth". The possible confusion of this wave type with focal processes and with other pathological rhythms was stressed.

4. A slow, posterior rhythm at 3 to 4 c/sec., which was sinusoidal in form and which occurred in long runs or continuously, was found in 1 per cent of the "abnormal" records. Sixty-two per cent of the patients showing this rhythm had experienced severe head trauma. Three out of five patients of this group exhibited symptoms of the type usually associated with emotional instability, and also showed a relatively high incidence of diencephalic signs and symptoms. Because of its manifest pathological significance this rhythm has been termed "slow posterior rhythm commonly associated with pathology". The importance of distinguishing this pathological rhythm from the slow alpha variant was emphasized.

5. A slow, posterior rhythm associated with petit mal was found in 0.5 per cent of the "abnormal" records. This occurred in paroxysmal bursts of high-voltage, 3 c/sec., sinusoidal waves and showed a close relationship to the typical 3 c/sec. wave-and-spike activity of petit mal.

6. Evidence for the diencephalic or brain stem regulation of the slow, posterior rhythms described was considered.

CONCLUSIONS

1. On a étudié l'incidence, les caractéristiques et les corrélations cliniques des rythmes postérieurs lents chez les tracés électroencéphalographiques de 8,000 malades « anormaux », et de 5,000 malades « normaux ». Quatre rythmes ou types d'ondes furent identifiés en nombre suffisant afin de permettre leur analyse. Des critères sévères furent établis pour chacun des types afin d'obtenir des groupes purs pour les fins de corrélation clinique.

2. On a trouvé chez un peu moins d'un pour cent des tracés « anormaux », et chez 0,2 pour cent des tracés « normaux », un rythme variant alpha lent qui démontrait une relation de fréquence de deux à un au rythme occipital sous-jacent. Puisqu'aucune corrélation ne pouvait être établie entre le rythme variant pur et une entité clinique quelconque, on a conclu que le variant alpha lent, tel que son nom l'indique, représente probablement une variation physiologique du rythme cortical de fond. On a trouvé chez plus de la moitié des malades dans ce groupe, des symptômes qui

sont généralement associés avec l'instabilité émotive. Cette corrélation suggestive avec un syndrome clinique confirme l'observation originale de Goodwin sur ce point, et soulève la question d'une dysfonction, probablement dans le diencéphale, ou dans les autres structures profondes. Aucune corrélation ne pouvait être établie avec la susceptibilité convulsive.

3. Des ondes lentes postérieures à 3 ou 4 c/sec. qui étaient asymétriques dans 50 pour cent des cas, et qui étaient caractérisés par une forme polyrythmique et « pointue », ou encore, qui apparaissaient sous forme d'ondes lentes isolées, étaient découvertes chez 17 pour cent du groupe « anormal » entre les âges de 6 et 25 ans, chez 9,9 pour cent du groupe « anormal » entre les âges de 16 et 25 ans, et chez 10 pour cent du groupe « normal » entre les âges de 19 et 22 ans. Quoique le terme de « rythme » ne peut pas, en toute justice, être appliqué à ce groupe, il porte néanmoins des traits distinctifs qui en font une entité électroencéphalographique reconnaissable. On a trouvé environ 85 pour cent des ondes de ce type chez des malades âgés de 6 à 25 ans. Puisque ce type d'onde ne montrait aucune corrélation avec aucune entité clinique particulière dans le groupe « anormal », et était découvert avec incidence égale chez les « normaux », on a conclu qu'il témoignait probablement des variations de maturation et de développement normaux. Pour cette raison on lui a donné le terme de « ondes lentes postérieures trouvés surtout chez les jeunes ». On souligne les possibilités de confusion de ce type d'onde avec des processus focaux, et avec d'autres rythmes pathologiques.

4. On a trouvé chez 1 pour cent des tracés « anormaux » un rythme lent, postérieur à 3 ou 4 c/sec., qui avait une forme sinusoïdale, et qui se manifestait sous forme de bouffées prolongées, ou de façon continue. Soixante-deux pour cent de malades avec ce rythme avaient subi des traumatismes crâniens sévères. Trois malades sur cinq, dans ce groupe, manifestaient des symptômes du type qu'on associe généralement avec l'instabilité émotionnelle, et montrait aussi une incidence relativement haute de signes et de symptômes diencéphaliques. A cause de sa signification pathologique manifeste ce rythme a été intitulé « rythme lent postérieur associé couramment avec la pathologie ». On souligne l'importance de la distinction de ce rythme pathologique avec le variant alpha lent.

5. Un rythme lent postérieur, associé au petit mal, était découvert dans 0,5 pour cent des tracés « anormaux ». Ceci se manifestait sous forme de bouffées paroxystiques d'ondes sinusoïdales à haut-voltage, et à 3 c/sec., et montrait un rapport proche à l'activité typique pointe-onde à 3 c/sec. du petit mal.

6. On étudie, enfin, l'évidence pour le règlement des rythmes lents postérieurs par le diencéphale ou le tronc cérébral.

ZUSAMMENFASSUNG

1. Die Häufigkeit, Charakteristica und klinischen Korrelationen von langsamen okzipitalen Rhythmen wurden bei 8000 Patienten und bei 500 normalen Individuen untersucht. Vier Arten von langsamen Rhythmen wurden identifiziert.

2. Langsame Alpha-Variante: Ein Rhythmus, dessen Frequenz die Hälfte des Alpharhythmus beträgt. Diese Rhythmusart hat keine spezifische Korrelation mit irgendwelcher klinischer Diagnose und wird deshalb als eine physiologische Variation betrachtet.

3. Langsame, oft asymmetrische, polyrhythmische oder vereinzelt auftretende Wellen in der Okzipitalregion mit einer Frequenz von 3 - 4 Hz. wurden hauptsächlich bei jüngeren Individuen gefunden. Keine spezifische Korrelation mit irgendwelcher klinischer Diagnose wurde festgestellt.

4. Langsame, sinusoidale, okzipitale Rhythmen mit einer Frequenz von 3 - 4 Hz., welche entweder kontinuierlich oder in langen Sequenzen auftraten, wurden hauptsächlich bei Patienten mit Zeichen pathologischer Gehirnveränderungen festgestellt (posttraumatische Syndrome, emotionale Labilität, dienzephale Störungen).

5. Ein langsamer okzipitaler Rhythmus, welcher mit Petit Mal-Attacken assoziiert war und in paroxysmalen Gruppen von hochgespannten sinusoidalen Wellen mit einer Frequenz von 3 Hz. auftrat, zeigte eine enge korrelation mit den typischen "Wave- and

Spike''- Entladungen mit einer Frequenz von 3 Hz., wie sie für Petit Mal-Anfälle charakteristisch sind.

6. Die Argumente, welche für eine dienzephale oder Hirnstammregulation der langsamen okzipitalen Rhythmen sprechen, werden besprochen.

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SPECIFIC ELECTROENCEPHALOGRAPHIC CHANGES WITH PENTOTHAL ACTIVATION IN PSYCHOTIC STATES

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The earliest report of the effect of barbiturate on the human EEG is that of Brazier and Finesinger (1945) who reported what are now well recognized changes resulting from injection of sodium Amytal, sodium pentobarbital, and sodium Pentothal intravenously in patients from the psychiatric department at Massachusetts General Hospital. There was no attempt to relate the findings to diagnostic categories or other specific clinical conditions. More recently a number of reports of the use of barbiturates to "activate" EEG changes have appeared. Among these is the report of Shagass (1957) on the "sedation threshold". Shagass has used sodium Amytal to produce fast activity in the frontal leads of the EEG and has measured the amount of the barbiturate necessary to produce these changes when associated with slurring of speech. He has developed an index of correlation between the amount of barbiturate necessary to produce this change and the presence of "anxiety". The problems of definition and semantics in his work have made it difficult for other workers to adopt the procedure whole-heartedly. Schneider and Thomalske (1956) used sodium Pentothal to bring to light abnormal activity resulting from sub-cortical lesions. They referred to work in progress for application of their technique in psychotic states. Roth and his co-workers (1957) found that the changes produced by electro-shock therapy in the electroencephalogram were much more clearly evident when the patient was given sodium Amytal intravenously. They correlated these changes with actual improvement in the psychotic state produced by the electro-shock therapy. M. Fink and his co-workers (1957) have results that are similar to those of Roth in correlating results of electro-shock therapy with delta waves in the electroencephalogram after injection of sodium Amytal.

Beginning in October, 1956, we have reported on the use of sodium Pentothal injection as an "activating" procedure for bringing to light otherwise unrevealed electroencephalographic changes in convulsive disorders and in psychotic states. This report will deal with the changes evident in psychotic states as compared with "normals" and contrasting illnesses. We have been particularly interested in contrasting "schizophrenic" with other types of psychotic reaction, particularly organic psychoses, and "normal" non-psychotic individuals. We are completely aware that the diagnostic entities used at present for statistical compilation and recording are fundamentally only descriptive and therefore may represent a number of different entities related only by superficial similarity of verbal and social behavior. We believe that this work represents a beginning in the direction of clearer differentiation of psychotic reactions, on the basis of recognizable physiologic differences.

TECHNIQUE

The patient is subjected to EEG recording in the usual manner, in our laboratory, reclining in bed. Standard 8 channel recording is always made preliminary to the Pentothal procedure. The present study is based upon monopolar records almost exclusively with the use of the "average" reference. The Pentothal is used as follows: the needle is placed securely in the vein. Recording is started and technical adequacy of the recording situation

is determined. While the recording is in progress, Pentothal is injected intravenously, 100 mg. at a dose, as rapidly as possible. The injection is accomplished in a period of 2 to 5 sec. usually. The cycle of effect produced by a single injection in most patients is completed within 1 to 2 min. After 2 min., the injection is repeated, and after the second cycle is repeated for the third time. The first two injections do not usually produce sleep or anesthesia. The third may produce sleep after a time. Unusual patients may require a fourth injection to produce maximal EEG changes. The timing of the injections is of maximum importance for the recognition of the changes to be described. Injections must be given rapidly to produce rapid development and decline of the Pentothal effect. The production of actual anesthesia is in no way desirable and is unlikely with this technique. The changes which can be observed during Pentothal anesthesia are in no way comparable to those produced by this technique in which time and amount of drug are sharply controlled. In pursuing the technique exactly as outlined, the useful EEG changes are usually exhausted after the second or third injection. The patients often go to sleep after the third injection and present a good sleep recording as a useful by-product of the Pentothal study. We have had no real difficulty with any patient given Pentothal by this technique. Occasional patients develop some salivation and require that the head be turned to one side or that an airway be used. Patients are ordinarily able to resume any usual activity within one-half hour to an hour following the procedure. The procedure may be repeated at intervals of two or more days without ill effect. The Pentothal effect is readily re-producible in individual patients except under conditions of special treatment which modify the patterns of activity.

OBSERVATIONS

Pentothal is the most rapidly effective and most rapidly destroyed of the barbiturates, so that cycles of effect can be produced without interference from sleep activity. The changes produced by Pentothal are the most "specific" produced by any of the barbiturates thus far investigated. Differences between the action of Pentothal and that of other barbiturates are illustrated in figure 1, A-D. Amytal sodium is a much "weaker" agent and produces its effects more slowly. Sodium Seconal and sodium pentobarbital are intermediate in activity between Pentothal and Amytal but have the serious disadvantage that patients are put to sleep before maximum specific effects are produced and that larger doses produce respiratory depression which requires cessation of the procedure. After injection of Amytal, pentobarbital and secobarbital, patients often sleep for a relatively long period, a practical disadvantage in carrying out an ambulatory procedure.

The changes produced by Pentothal have, under the strict conditions of this procedure, definite time relationships and qualitative characteristics which can be related to the clinical condition of the patient. "Normal" individuals are clearly distinguishable from the "Pathologic". It is not unexpected that some normal individuals may show effects bordering on those evident in the psychotic and otherwise pathologic population, yet by strict criteria these can be clearly differentiated (fig. 2, A-D).

Early in our work, it was evident that many or our "Schizophrenic" patients were showing activity different from that evident in other groups under the influence of Pentothal. The confirmation and validation of these early observations are the chief purposes of the present report. Over 200 patients classified as "schizophrenic" by the hospital staff entirely independent of EEG observations, are compared with almost 200 EEG observations in "non-schizophrenic" and "normal" individuals. The "non-schizophrenic" patients were chiefly "organic" psychotic individuals and patients in the "personality disorder" (psychopathic) groups. The normal individuals were individuals on the hospital staff, chiefly young adults who submitted voluntarily to the EEG investigation under Pentothal.

The characteristics which were found in the "schizophrenic" patients were: (1) ac-

centuated beta activity of more than 25 μV. amplitude which lasted much longer than beta activity in "non-schizophrenic" following Pentothal injection. (2) "Bursts" of fast activity consisting of groups of waves more than 10 times the amplitude of background activity, of 25 μV. to more than 100 μV., with a frequency over 15 per sec., not less than 0.25 sec. but often more than 1 sec. in duration. (3) "Theta" activity of more than 100 μV. amplitude, synchronous in two or more leads, occurring early following the in-

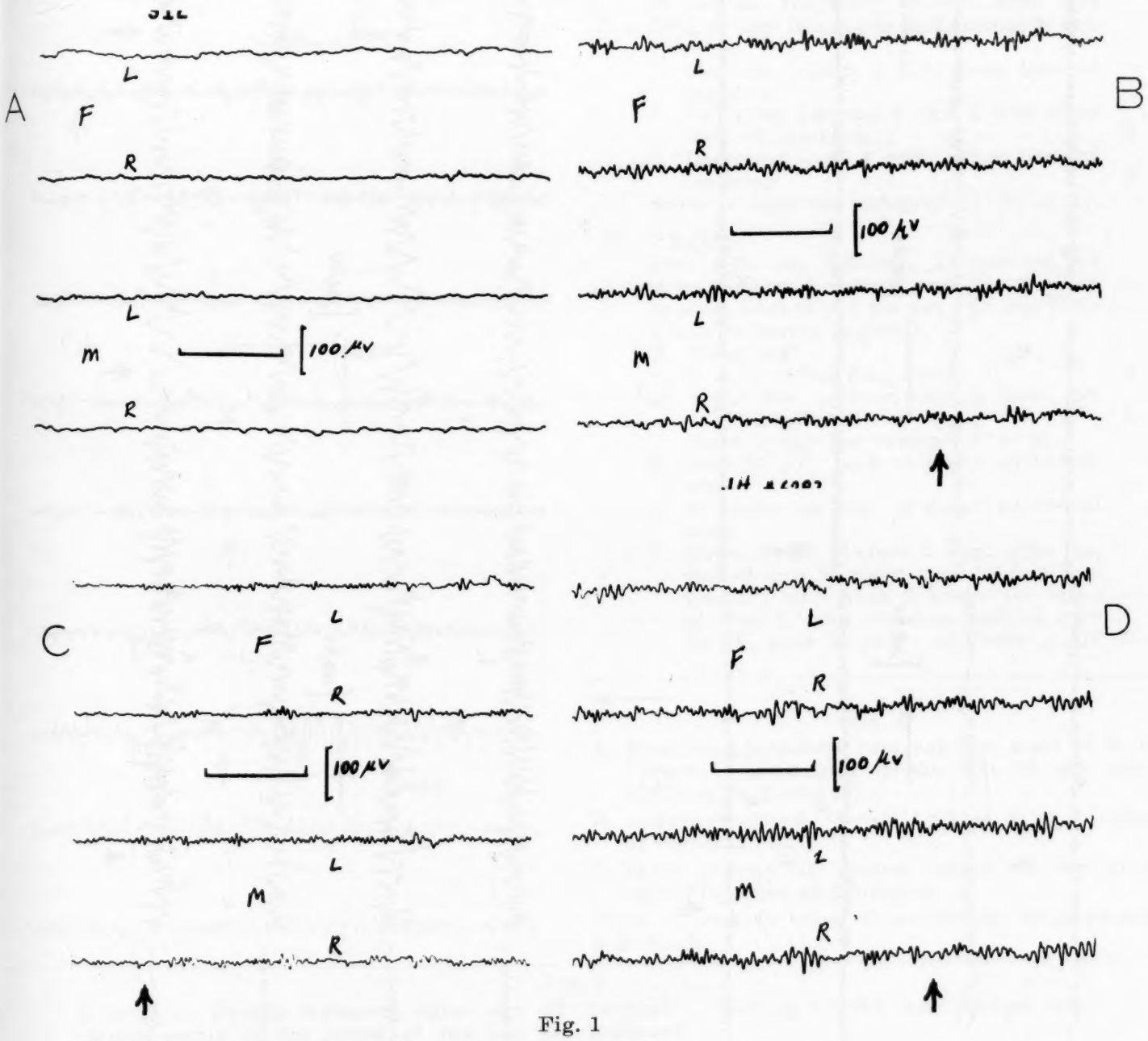


Fig. 1

EEG of "normal", non-psychotic employee, male, age 21.

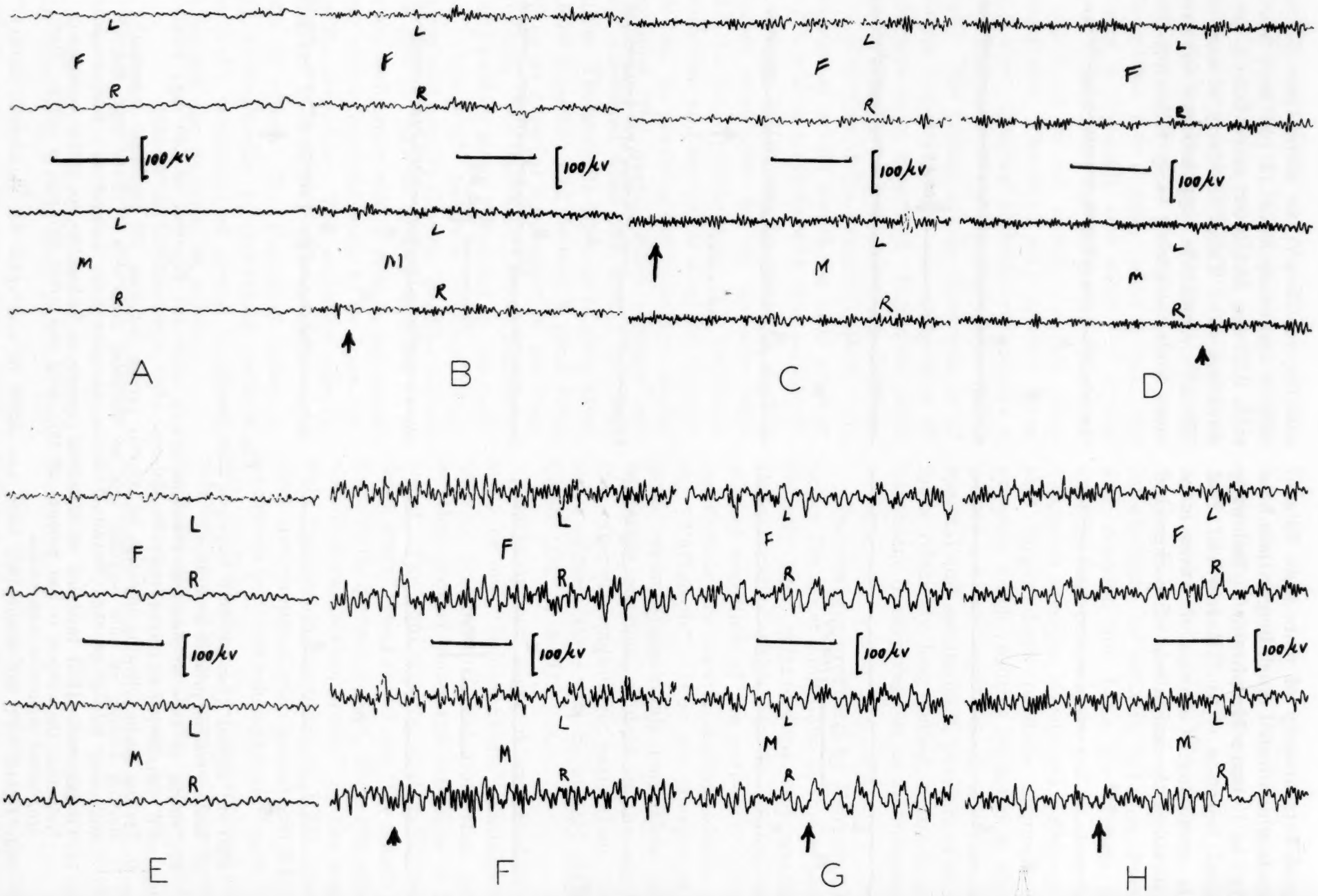
A. Resting tracing prior to medication.

B. Tracing at time of maximal Pentothal effect, after 3rd injection of 100 mg., total 300 mg. Pentothal (arrow indicates 130 sec. after injection).

C. Tracing made following injection of Amytal (arrow indicates 130 sec. after injection). Resting tracing on this occasion was no different from "A". Note that Amytal has much less effect than Pentothal within the same time interval and dose range.

D. Tracing made after injection of Nembutal (arrow indicates 130 sec. after injection). Note that the subject is less tolerant of this drug and after 200 mg. is asleep. More drug would embarrass respirations.

Only frontal (F) and motor (M) leads are shown to save space for significant activity which is evident in these leads predominantly.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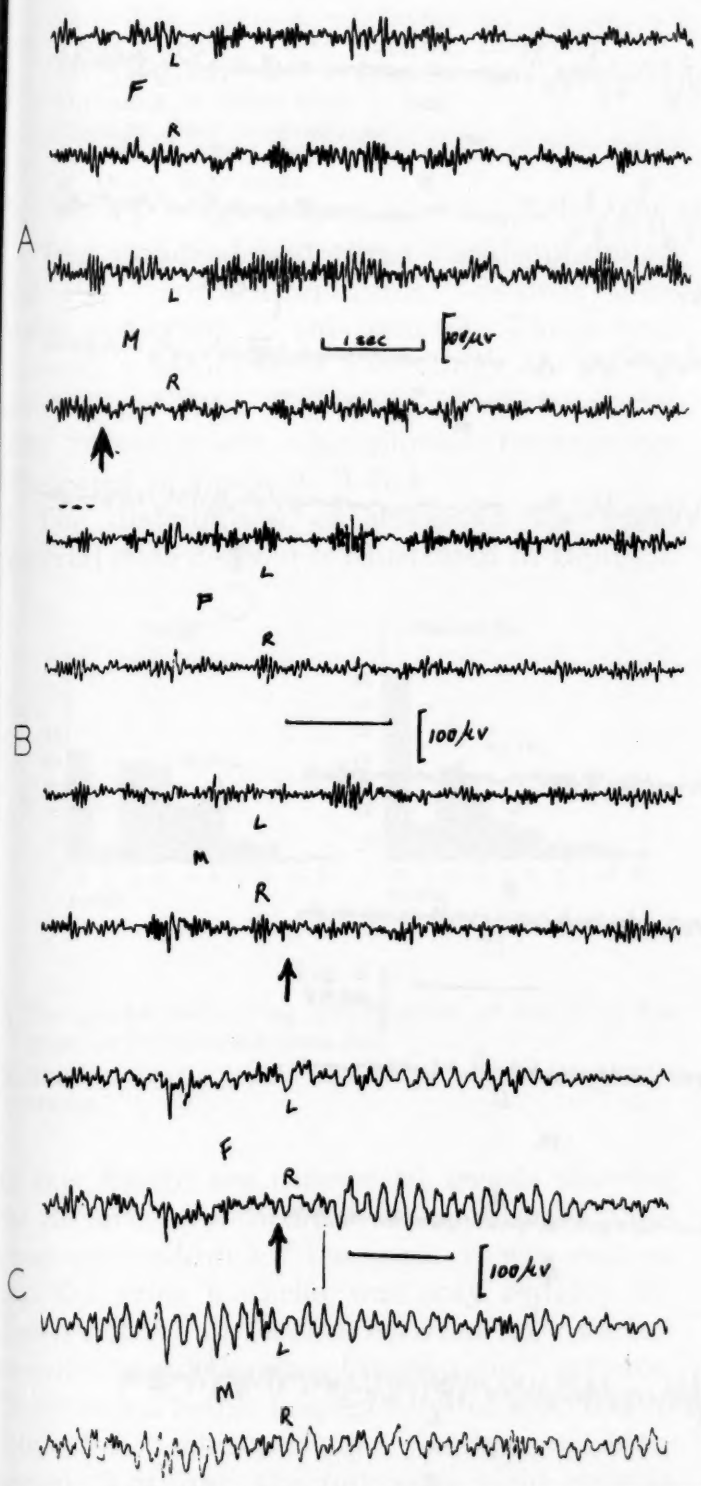


jection of Pentothal, usually within the first 30 sec., and later giving way to the faster forms of response (fig. 3, A, B, C).

To fit these changes into a kind of quantitative scheme the following scoring criteria were set up:

	Score
I. "Beta Activity"	
20 per sec. frequency or over, more than 50% of time in any one lead, during 30 sec. episodes.	
1. Occuring within 2 min. from time of injection.	1
2. Occurring between 2 and 4 min. from time of injection.	2
3. Occurring over 4 min. after time of injection.	3
Score in only one category (1, 2, or 3).	
II. "Bursts"	
Over 0.25 sec. duration, 15 per sec. or more frequency, voltage over 25 μV. peak to peak, more than 6 per min., present after 1 min. following injection.	
A. Duration	
1. 0.25 to 0.6 sec., score	1
2. 0.6 sec. or over, two or more per min., score	2
Score in only one category (1 or 2).	
B. Over 50 μV., peak to peak: additional score	1
C. 15 bursts per min. or more: additional score	1
D. Extra credit: before 1 min. after injection only if above qualifications are present; more than 5 bursts per min., all over 0.5 sec. duration, and all over 50 μV. peak to peak: additional score	2

Fig. 3

A. Illustrates persistent beta activity, some of it in "bursts" as defined in the text 75 sec. after injection of Pentothal.

B. Clearly developed "bursts" 85 sec. after injection of Pentothal.

C. Theta activity of scoring degree, 14 sec. after second injection of Pentothal.

These 3 records were from clearly schizophrenic individuals.

Fig. 2

A to D — Female registered nurse, age 25 "normal". Resting tracing and changes at various points in the course of the test are indicated.

A. Resting tracing.

B. 38 sec. after 1st dose of Pentothal, 100 mg. showing minimal effect.

C. 15 sec. after 3rd dose of Pentothal, 100 mg., total 300 mg. in an interval of approximately 4 min. The onset of the Pentothal effect as the medication arrives in the brain is shown.

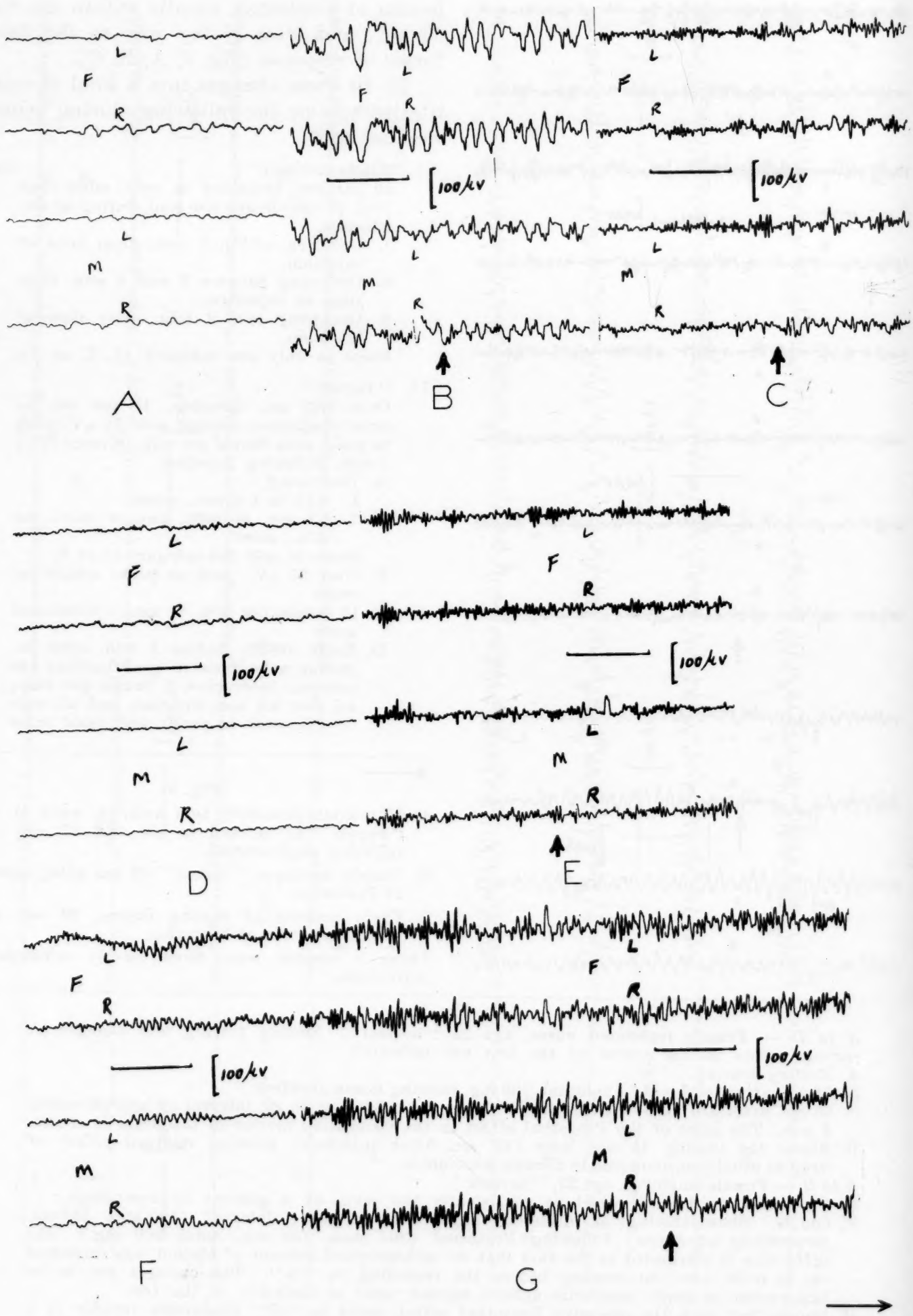
D. Shows the tracing 48 sec. later (63 sec. after injection) showing minimal effect of drug as usually encountered in normal individuals.

E to H — Female employee, age 23, "normal".

E. Shows resting tracing which is consistently the same on a number of recordings.

F. and G. Show tracing on different days, but the same interval (40 and 35 sec. respectively at arrow) following Pentothal (2nd dose 100 mg., total 200 mg.) The difference is attributed to the fact that an undetermined amount of alcohol was consumed up to 3:00 a.m. the evening before the recording in "G". The changes are to be interpreted as early anesthetic effects beyond what is desirable in the test.

H. Shows that even the excessive Pentothal effect noted in "G" diminishes rapidly in a "normal" individual (40 sec. after "G").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III. Theta activity — 4 to 7 per sec. frequency, very regular, over 1 sec. duration, synchronous in more than 1 lead.
Voltage peak to peak, μV.:
1. 100 to 200, score 1
2. Over 200, score 2
Score in only 1 category (1 or 2).

Two hundred and three "schizophrenic" and 193 "non-schizophrenic" records were scored according to this scheme. These were in every instance first recordings on the individual patients. Examples of what we consider characteristic schizophrenic tracings are illustrated in figure 4, A-G.

The distribution of scores in the gross material thus derived is illustrated in figure 5.

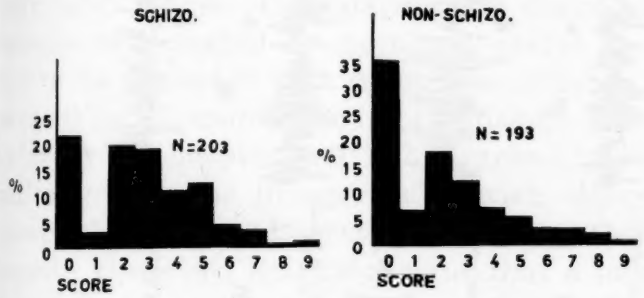


Fig. 5

A. Bar graph indicating distribution of scores in the gross schizophrenic material.
B. Similar bar graph showing non-schizophrenic scores.

In this figure are illustrated trends showing the difference between "schizophrenic" and "non-schizophrenic" tracings. It was evident that the gross material was only roughly indicative of the difference between the "schizophrenic" and "non-schizophrenic" groups. To achieve a better homogeneity of material in both the "schizophrenic" and non-schizophrenic" groups, the following rigid criteria were applied: only patients admitted in the years 1956 and 1957, between ages 15 and 45 years, not previously treated for their illness (for this the previous records of the patients were individually, diligently searched out) and with adequate EEG recordings were used in the compilation. This left 14 patients in the "schizophrenic" group and 31 in the "non-schizophrenic" group. In this "refined" material, there is clear distinction between "schizophrenic" (high scores) and "non-schizophrenic" groups (low scores). Application of "chi-square" and "T" calculations to this material indicated a difference between the two groups at the 1 per cent level of confidence. This is shown in figure 6.

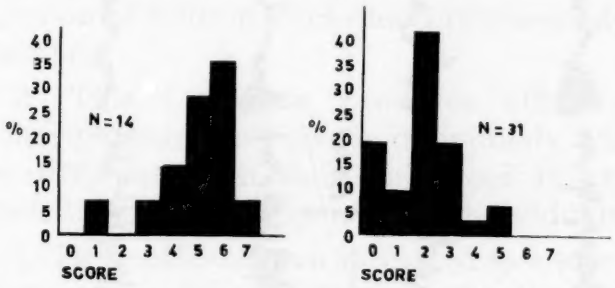


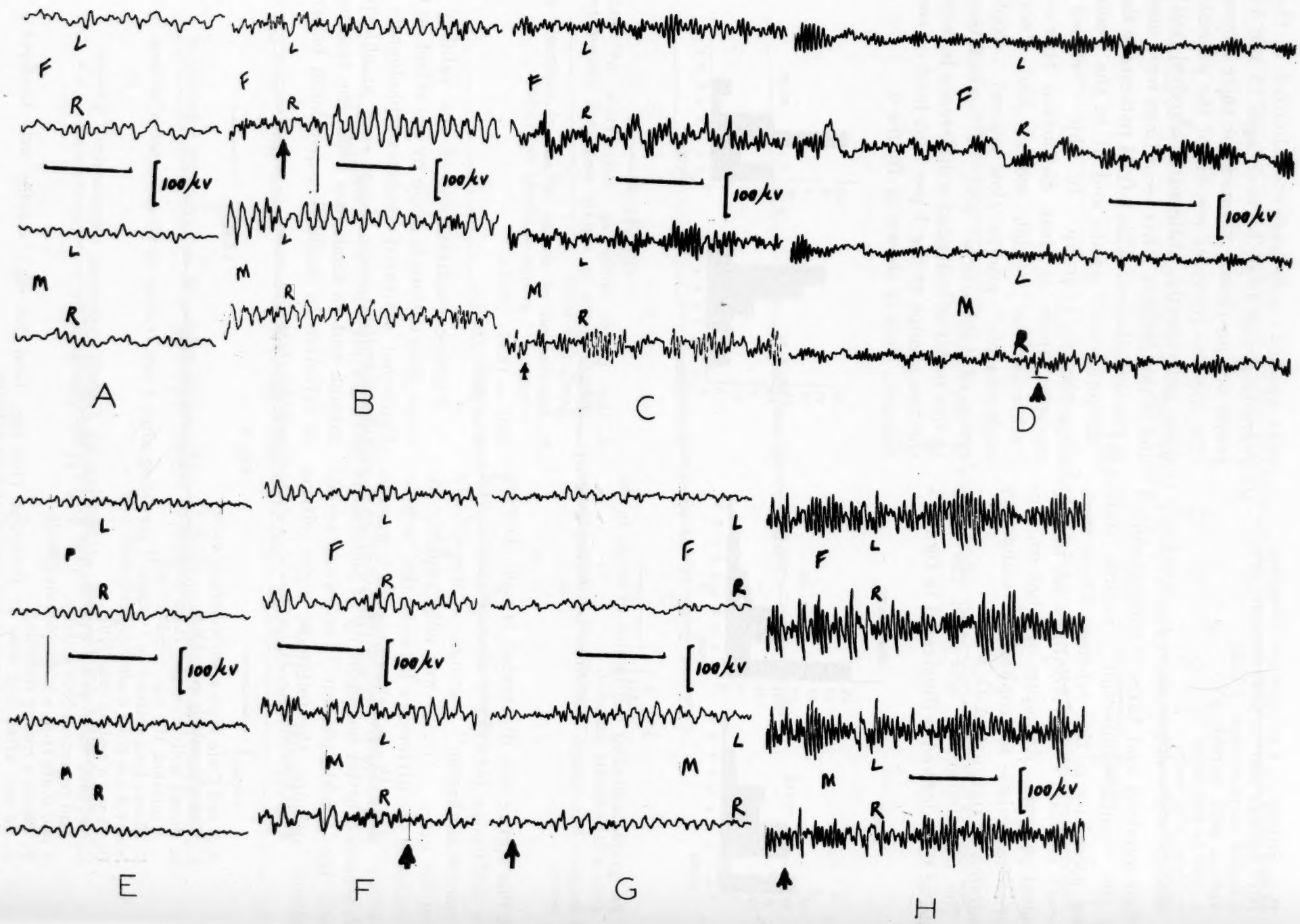
Fig. 6

A. Bar graph indicating distribution of schizophrenic scores in rigidly restricted schizophrenic group (see text).
B. Distribution of scores in non-schizophrenic and "normal" groups similarly restricted.
$Chi^2 = 18.47$: (0.01).
$T = 8.05$: (0.01)

Further confirmation of the validity of these observations is given by the effect on the Pentothal activated electroencephalogram of therapy with newer drugs such as chlorpromazine and its analogues when the treatment is effective in modifying psychotic behavior

Fig. 4

A, B and C are from a schizophrenic male.
A. Shows a resting recording.
B. Shows well developed theta activity of characteristic degree, 36 sec. after 3rd injection of Pentothal, 100 mg., total 300 mg.
C. Shows beta activity in "bursts" persisting after 1 min. (arrow at 60 sec. after injectiong.
D and E are from a schizophrenic male.
D. Shows a resting recording.
E. 120 sec. after 2nd injection of 100 mg. of Pentothal showing asymmetrical "bursts" and persistent beta activity.
F and G are from a schizophrenic female.
F. Shows a resting recording.
G. 85 sec. after 2nd dose of Pentothal (100 mg., total 200 mg.) showing well developed asymmetrical "bursts" and persistent beta activity.



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patterns. Liberson (1955) showed that chlorpromazine has little or no effect on the resting "awake" EEG. With the help of Pentothal activation, however, we have found a clear difference between the pre-treatment and treatment EEG's. The elimination of the "schizophrenic" characteristic does not develop rapidly, but takes from 1 to 3 or more months to become evident. Two examples of the changes which have been observed in over 80 patients thus far are illustrated in figures 7 and 8.

The specific effect of intensive medication used over a long period of time can be regularly demonstrated, and that this effect is related to favorable change in symptoms of psychotic illness. Considering the diagnostic morass represented by psychotic states, it is not to be expected that diagnostic criteria at present in use under varying conditions ("ambulatory", "hospitalized", "disturbed", etc.) will regularly be in agreement with electroencephalographic observations as we have found. However, it is important that a large proportion of psychotic patients hospitalized for such illness can be found to have "specific" EEG activity which is correlated with clinical response to drug therapy. It is hoped that this technique when combined with other forms of investigation will help to establish psychiatric diagnosis on the basis of objective and measurable changes.

Technically, the mechanisms involved in this method of using Pentothal to reveal otherwise unavailable EEG activity may be explained in a number of ways. The idea of a simple threshold phenomenon seems least acceptable since too many individuals ("non-schizophrenic") never show the changes described. Evidence is accumulating for future documentation that these changes represent true sub-cortical activity. It is considered sufficient for the present, however, simply to report the observations and their immediate implications, since these have, at the present time, greater interest than the possible mechanism involved.

CONCLUSIONS

1. A technique of EEG activation using injection of sodium Pentothal intravenously is described.

2. This technique produces effects in "schizophrenic" psychotic individuals which are different from those produced in other psychotic states and in normal individuals.

3. These effects were subjected to a scoring scheme to produce roughly quantitative data. With such data the difference between the "schizophrenic" and "non-schizophrenic" was shown to be statistically significant.

4. The effects of Pentothal activation which are present in the active psychotic state, can no longer be produced when the patient has improved under therapy with chlorpromazine or similar drugs.

Fig. 7

Shows course of EEG changes in a patient who showed marked improvement under treatment with chlorpromazine and the recurrence of the EEG changes with a relapse of the illness when medication was discontinued.

A to E show pre-treatment tracing.

A. Resting tracing.

B. Theta activity of scorable degree, 14 sec. after 2nd injection of Pentothal, 75 mg., total 150 mg.

C and D — Beta activity and "bursts", after 3rd injection of Pentothal, 75 mg., total 225 mg. C 23 sec. after injection with marked "bursts", and D 67 sec. after injection showing persistence of "bursts" and beta activity.

E, F and G — Show the EEG studies under treatment with chlorpromazine.

E. Resting tracing not appreciably different from the pre-treatment level.

F. Maximum theta effect much less developed than before treatment, 35 sec. after 2nd injection of Pentothal, 75 mg., total 150 mg.

G. Practical absence of beta activity and "bursts" of scorable degree, 120 sec. after 2nd injection of Pentothal 75 mg., total 150 mg.

H. Shows condition at the time of return to the hospital 8 months later in marked relapse of schizophrenic symptoms. Patient had gained at least 30 lbs. in weight over period of observation, so each dose of Pentothal was increased from 75 to 100 mg.; shows maximal beta and "burst" activity, 72 sec. after 2nd injection of Pentothal, 100 mg., total 200 mg.

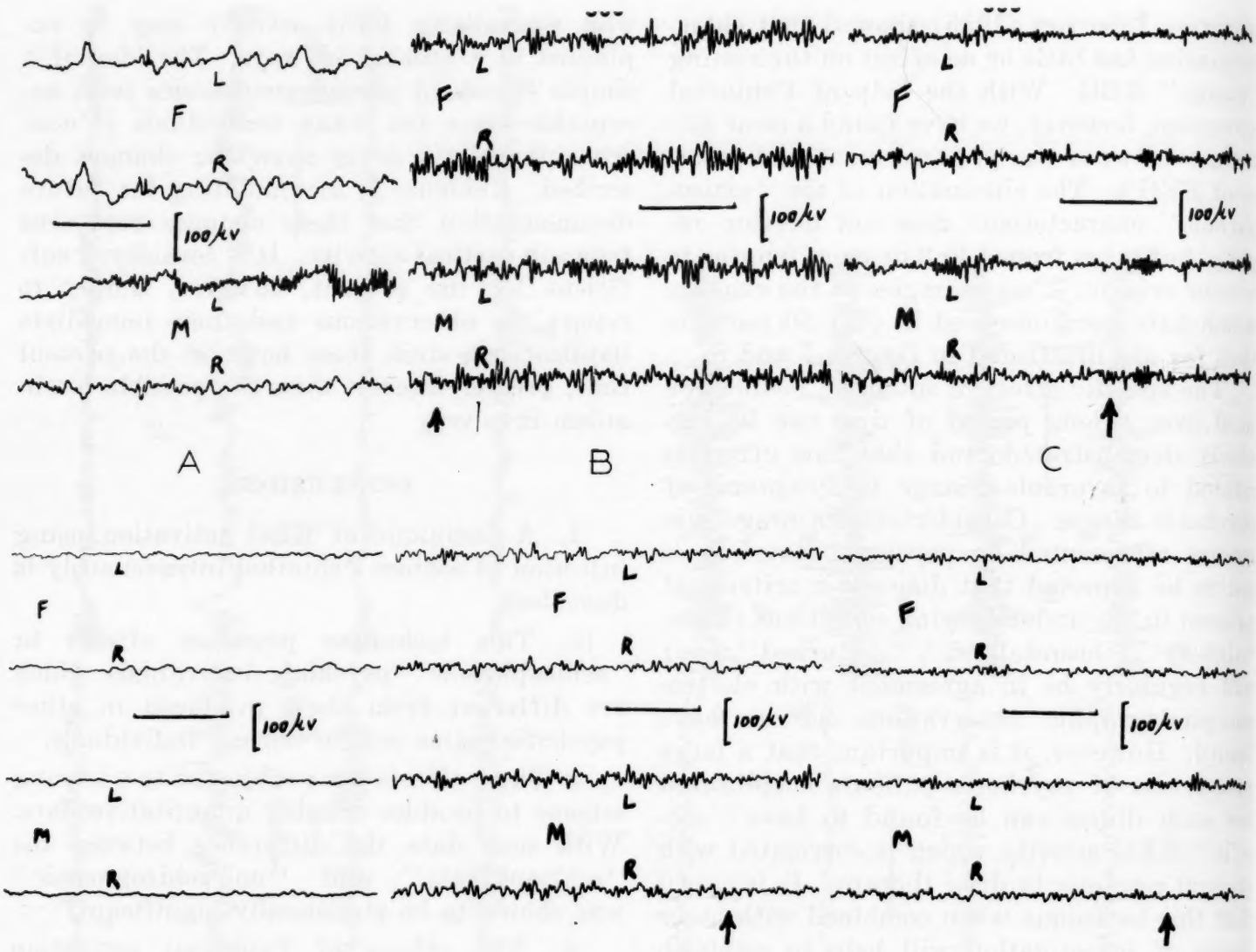

Fig. 8

Similar schizophrenic patient, age 14. Patient was highly uncooperative and "wild" as indicated in the marked artefact, in "A".

B. Shows tracing 36 sec. after 2nd dose of Pentothal with marked "bursts" and beta activity.

C. Shows persistent "bursts" and beta activity 112 sec. after Pentothal. This patient was undernourished and only 50 mg. Pentothal was given each injection.

F, E, F same patient after the psychotic condition was relieved by Prochlorperazine (Compazine).

D. Resting treacing which is unremarkable.

E. Shows the tracing 36 sec. after 2nd dose of Pentothal with no more than the normal barbiturate effect.

F. 110 sec. after 2nd dose of Pentothal similarly showing minimal barbiturate effect.

E and F are to be contrasted with B and C.

RÉSUMÉ

On décrit une technique d'activation EEG en utilisant l'injection intra-veineuse de Pentothal sodique.

2. Cette technique produit chez des individus psychotiques « schizophréniques » des effets qui sont différents de ceux produits dans d'autres états psychotiques et de ceux de l'individu normal.

3. Ces résultats furent reproduits sur un tableau échelle afin de produire des données grossièrement quantitatives. Avec de pareilles données on a pu démontrer que la différence entre les «schizophréniques » et les « non-schizophréniques » était statistiquement significative.

4. Les effets de l'activation au Pentothal qui sont présents dans l'état psychotique actif

ne peuvent plus être reproduits lorsque le malade s'est amélioré sous l'effet du chlorpromazine ou d'une médication analogue.

ZUSAMMENFASSUNG

1. Eine Methode der EEG-Aktivierung mit intravenöser Injektion von Pentotal Natrium wird beschrieben.

2. Dieses Vorgehen erzeugt bei schizophrenen Patienten Effekte, welche verschieden sind von denjenigen, welche man in anderen psychotischen Zuständen oder in normalen Individuen beobachten kann.

3. Diese Effekte wurden Kriterien unterworfen, welche eine quantitative Analyse erlaubten. Die so erhobene Befunde zeigten, dass der Unterschied zwischen Schizophrenen und Nicht-Schizophrenen statistisch signifikant ist.

4. Die Effekte von Pentotalaktivierung, welche im aktiven psychotischen Stadium vorhanden sind, können nicht mehr produziert werden, wenn der Zustand des Patienten sich unter dem Einfluss einer Chlorpromazinbehandlung oder demjenigen einer Therapie mit ähnlichen Medikamenten gebessert hat.

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ANNOUNCEMENT

5th INTERNATIONAL CONGRESS OF SOCIETIES FOR EEG AND CLINICAL NEUROPHYSIOLOGY
to be held in Rome
September 7th to 13th, 1961

In accordance with the decision taken at the 4th International Congress of Societies for EEG and Clinical Neurophysiology held in Brussels in July 1957, the 5th International EEG Congress will be held at Rome, not as a member of an International Congress of Neurological Sciences, but in relation only to the 7th International Congress of Neurology. As recommended by the assembly, the EEG Congress will retain a certain degree of autonomy but there will be several days of overlap during which topics of joint interest will be discussed. The official languages of the Congress are to be English and French.

The Organizing Committee duly constituted under the by-laws of the International Federation met on October 10th, 1959, in Marseille. After due deliberation, this committee drew up the provisional program outlined below. There will be five sessions, each devoted to a chosen topic in EEG, two days of joint sessions with the Congress of Neurology, and one day allotted to free communications of EEG interest.

The following subjects have been chosen for main conference topics:

1. The Neurophysiological Basis of the EEG.
2. Intracerebral Electrography in Man.
3. EEG in Non-epileptic Paroxysmal Disturbances.
4. EEG in Sleep.
5. EEG in Phylogeny.
6. EEG and the Physiology of Behaviour.
7. The Analysis and Display of EEG Information.

The joint sessions with the Congress of Neurology will include:

1. The EEG aspects of Cardiovascular and Respiratory disorders.
2. The EEG in Inborn Disorders of Metabolism.

One whole day will be devoted to the presentation of short papers; if an excessive number of these is received they may be grouped and presented in the form of digests.

As required by statute the Executive Committee and the General Assembly will meet at the time of the Congress.

All communications should be addressed to:

Dr. R. Vizioli,
Clinica della Malattie nervose e mentali,
Viale dell'Universita 30,
ROME, ITALY.

Immediately preceding the Congress an Advanced Course in Electroencephalography will be held in Marseille. (See separate announcement, page 732).

THE RELATION BETWEEN THE FREQUENCY OF THE ALPHA-RHYTHM AND THE SPEED OF WRITING

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(Received for publication: March 1, 1958)

PRELIMINARY REMARKS

In psychiatric diagnosis and in psychological studies it appears to be of interest to investigate the possibility of arriving at a generalized concept of speed on the basis of correlating existing concepts such as the working-speed, psychomotor speed, the pace of living and possibly, among other things, also the speed of physiological processes. This possibility exists if these entities or at least the majority of them show a reasonable correlation, thus ensuring that knowledge of generalized "speed" will give an insight into the magnitude of the different speeds.

It seems likely that some of the speeds mentioned above are related, as they are often determined by the speed of action in experimental situations. Therefore, they have an element in common, e.g. activities, which call on similar or identical mechanisms. Various authors have shown that some of the speeds cited above indeed do show a correlation (Takala 1953; Frischeisen-Köhler 1933).

Investigations have also been carried out into possible correlations of psychomotor speed with a prominent physiological rhythm: the alpha-rhythm.

Kibbler, Boreham and Richter (1949), Kibbler and Richter (1950), Walsh (1952, 1953) and Lansing (1957) investigated the relation between the moment of action and the phase of the alpha waves. Kibbler *et al.* found evidence that the moment of action is related to the phase of the alpha waves. Their findings, however, were not supported. Moreover, in a communication by Lansing attention was drawn to the frequency of the alpha rhythm. He concluded that no consistent relationships were observed between reaction time and frequency or amplitude of the alpha rhythm.

Experiments in this direction have also been carried out by Mundy-Castle, Biesheuvel and Pitt (1953). Their experiments concerned relationships between alpha frequencies and psychomotor speeds. In fact they found relations between some of these speeds and the alpha frequency, but no relation between alpha frequency and speed of writing. The common element in the diverse speeds and the frequency of the alpha rhythm was indicated by them as unstructured motor speed.

Kraepelin (see Kretschmer 1955, 1956) drew attention to the importance of the examination of the pressure applied during writing. Steinwachs *et al.* recently have developed a more accurate method for recording this pressure. Moreover they presented criteria for the evaluation of the results. It seemed interesting to investigate if the use of this new technique and criteria would enable us to establish a relation between alpha frequency and the speed of writing. Moreover, in this clinic an apparatus is available which is well suited for an investigation of the alpha rhythm, especially of its frequencies.

If certain criteria are applied in selecting the test subjects, it is possible to establish a close connection between writing speed and the frequency of the alpha rhythm. This connection may be expressed in a quantitative relation. If, however, the test subjects are not selected according to these criteria, the writing speed and the alpha frequencies are but loosely related.

Russel-Davis (1946) concluded from his investigations that the adjustment and attitude of the test subjects with regard to difficult situations is expressed in the behaviour and speed in which they executed certain tests. Therefore, we investigated also whether cer-

tain common personality features were present in subjects, whose writing speed was slow but relatively fast in comparison with the alpha frequencies. Our conclusion is that such common features may indeed be indicated.

METHODS

A. The electroencephalogram was recorded in the usual way. An eight channel electroencephalograph (type Grass) was used in combination with a frequency-analyzer. The latter consisted of eleven selective filters (quality-factor Q = 10), tuned to different frequencies. One EEG channel was fed into the analyzer; the output-signals were recorded by 11 pens. Thus a precise determination was obtained of the frequency of the alpha rhythm, also in cases where it was almost indiscernible in the primary EEG tracing. Furthermore a good overall picture was obtained of fluctuations of the frequency. These fluctuations were of importance for determinating the average value.

As the investigation was done with patients from a psychiatric clinic, it is evident that a relatively large number of electroencephalograms was abnormal. The degree of abnormality is difficult to determine. To obtain a notion about the abnormality, each electroencephalogram was also assessed as to the presence of slow frequencies (delta and theta rhythms). A division into two groups was made:

1. Theta and delta rhythms not discernible, or with such small amplitudes as may occur also in many ''normal'' subjects.

2. Theta and delta rhythms clearly present respectively predominant in the EEG.

B. To determine the writing speed, the subject was asked to write a number of times the testword ''momom'' on a small table. This table was suspended on springs. The displacement could be recorded as a function of time (Steinwachs 1952). Some training preceded the recording. As a measure for the time of writing, only the time in which the subject actually wrote was calculated, hesitations or interruptions in the writing were discounted. People physically unfit for normal writing were not used for these experiments. Because the time of writing per word is not altogether constant (dispersion of about 6 per cent) an average value was determined as was done also with the frequency of the alpha rhythm.

The time of writing doubtlessly depends also on the extent to which the test subject is used to writing. According to Steinwachs *et al.* (1952), this is expressed, among other things, in the regularity of the writing and the number of interruptions in the writing of a single word. In view of this, a division into two groups was made.

The first group contained the patients who wrote with two interruptions per word or less, the second group contained the patients who wrote with more interruptions or very irregularly (dysrhythmically). As to the latter group, according to Steinwachs, one may speak of abnormal motor mechanisms of writing.

OBSERVATIONS AND CONCLUSIONS

A. In figure 1 the results of all observations are presented. Figure 2 gives only those observations which are related to subjects whose motor mechanism of writing and EEG are both ''normal'' (see Methods). Within the group selected in this way there is a striking correlation between frequency of the alpha rhythm and the speed of writing. Generally spoken the speed of writing increases with the frequency of the alpha rhythm.

This correlation has been investigated with Kendall's rank-correlation test (Kendall 1955). For the application of this test a measure for the correlation has to be computed, namely the rank-correlation coefficient of Kendall; this is a quantity, which may vary between -1 and $+1$. The coefficient is $+1$ if one datum always increases or decreases along with the other datum. It is -1 if one datum always increases when the other decreases and inversely. If the measured quantities are independent, the coefficient in most cases is about zero. In the present case a value of $+0.59$ was found for the rank-correlation coefficient. The probability distribution of Kendall's coefficient, under the hypothesis that the quantities measured are independent, is known. This distribution does not depend on the ways both quantities are distributed,

but only on the number of observations made. The probability then that the rank correlation deviates at least 0.59 from zero is called probability of exceedance k. This probability now can be computed. If k is sufficiently small — in practice the boundary (level of significance) is often fixed on 0.05 or 0.01 — the assumption of independence is rejected. In the present investigation $k < 0.001$ was found. Thence the hypothesis of independence may confidently be rejected and the existence of a correlation may be inferred.

The measure commonly used for correlation is the coefficient of correlation of Pearson. This measure assumes likewise values between -1 and $+1$; the extreme values are only attained when the points observed lie on a straight line. The coefficient is here 0.84, indicating that the points lie grouped rather well along a straight line. With this coefficient it is much more difficult to determine a probability of exceedance as its probability distribution also in case of independence of the quantities depends here on the unknown type of the distribution of these quantities.

We may conclude at present that there is a relation between the frequency of the alpha rhythm and the speed of writing in the population of persons for which the sample is representative (patients from the psychiatric clinic with ''normal'' EEG and motor mechanism of writing). Since it is improbable that there would be a direct connection between the speed of writing and the frequency of the alpha rhythm, one or more factors determining the frequency of the alpha rhythm do likewise influence the speed of writing. There is no reason to suppose, that this would apply only to the selected group (patients) considered here, so that the above conclusion may be expected to be of general validity.

B. It is striking that, unless the subjects are selected according to the criteria indicated, there is hardly any correlation between the two quantities investigated. Should an important role be played by other factors than those determining the detected relation between alpha rhythm and speed of writing, this is evidently expressed by deviating motor mechanisms of writing or by an abnormal EEG or by both.

Starting from the assumption, that the relation between the frequency of the alpha rhythm and the speed of writing is given for ''normals'' by the line of regression in figure 2, the subjects may be divided into the following two groups:

1. A group which writes too fast with regard to its alpha rhythm.

2. A group which writes too slowly with regard to its alpha rhythm.

An attempt has been made to trace whether the subjects of both groups possess different personality traits. The purpose was to establish from the diagnosis, whether the patient in an experimental or other situation would react with an ''overactivity'' reaction (O) or with a ''withdrawal'' reaction (W).

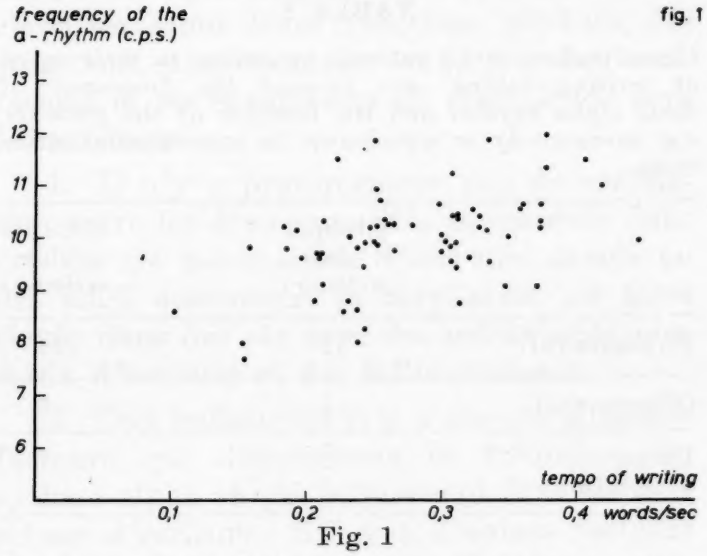

fig. 1

Fig. 1

Frequency of the alpha rhythm versus speed of writing. Results of 69 unselected patients from the psychiatric and neurologic clinic.

We made this classification with regard to an investigation by Russel-Davis, who examined a large number of R.A.F. pilots and, in view of their behaviour, arrived at the above classification.

The ''over-activity'' reaction is demonstrated by a strained attitude, perseverance, emotional disturbances, preoccupation, physical symptoms in the form of vasolability and fast increase of activity during a test.

The ''withdrawal'' reaction is demonstrated by indifference, boredom and discon-

tent, leading not to activity but to apathy. It appeared that the greater part of the patients, reacting with an ''over-activity'' reaction belonged to group 1, those with a ''withdrawal'' reaction to group 2.

Since such a division is rather subjective, 45 of the patients chosen at random were independently classified anew by two psychiatrists, this time according to their clinical picture. Both appreciations have been combined, in such a way that a patient was classified as belonging to the O-group (over-activity) if both psychiatrists put him in this group or if one did so, while the other one marked him down as a dubious case, and so

TABLE I

Classification of 45 patients according to their speed of writing taking into account the frequency of their alpha rhythm and the reaction of the patients, e.g. overactivity or withdrawal in experimental situations.

	Group 1 (fast writing)	Group 2 (slow writing)
W(ithdrawal)	12	14
O(bsessional)	7	3
Doubt k = 0.18	2	7

on (see table I). From this table it appears that a relatively larger number of the O-group belongs to group 1 and of the W-group to group 2. If the patients ultimately marked with ''doubt'' are left out, this leaves a division in two groups (a double dichotomy). A possible relation between both divisions may be investigated by Fisher's test for independence in a 2 x 2 table (Fisher 1954).

Again a measure for the relation between both divisions is computed and from this a probability of exceedance k is determined. This is the probability that the measure will assume the value found or a less probable one, calculated on the presumption that the divisions are independent. The value of k was found to be > 0.05 and therefore the hypothesis of independence cannot be rejected.

A third psychiatrist classified the patients according to their ''fight'' and ''flight'' re-

TABLE II

Classification of 45 patients according to their speed of writing taking into account the frequency of their alpha rhythm and the reaction of the patients, e.g. fight or flight in experimental situations.

	Group 1 (fast writing)	Group 2 (slow writing)
Flight	7	13
Fight	11	10
Doubt k = 0.04	3	1

actions (Bastiaans 1957), a division with a rather close analogy to that of Russel-Davis. On the strength of this division (see table II) the assumption of independence can be rejected. In this case the probability of exceedance mentioned above was $k = 0.04$.

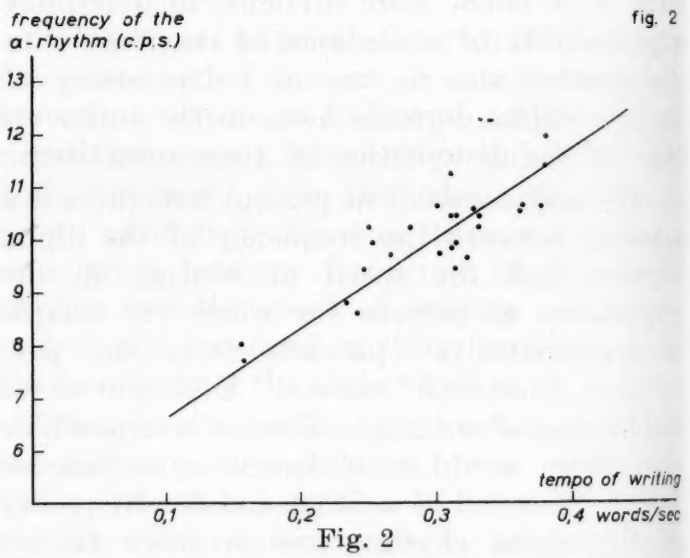

fig. 2

Fig. 2

Frequency of the alpha rhythm and speed of writing. **Result of patients with ''normal'' EEG and ''normal'' motor mechanisms of writing.**

DISCUSSION

The relation found between writing speed and frequency of alpha rhythm may give rise to speculations about its cause. Further research will have to decide whether a driving action of the alpha rhythm may be assumed or whether identical nerve-paths and -centres are engaged in the processes. A third possibility might be that cerebral entities engaged in different processes may be influenced in the same direction by qualities and conditions of the brain-tissue (degree of dispersion, me-

tabolic conditions and similar factors). Probably closely related to this is the question whether it makes sense at all to speak of "the speed", a question which at this stage cannot yet be answered.

The relation between frequencies of alpha rhythm and psychomotor speed may improve the meaning and use of this measure. Since a large range of variations is considered normal in the frequency of the alpha rhythm this will also bear upon the psychomotor speed. Besides, the causes of extreme psychomotor speed will have to be sought in quite different directions, depending on the frequency of the alpha rhythms with regard to the quantitative relation indicated. In the case of non-agreement, a statement about certain personality traits of the subject may be put forward with some plausibility. However, as the correlation is as yet low, the value in practice is small.

Of course the difficulty remains that factors like the habit of writing ("eingeschliffen sein" of the writing (Kretschmer)) among other things will always make their influence felt and that the regression line shown in figure 2 need not always be wholly representative for an individual test subject.

SUMMARY

The frequency of the alpha rhythm and of the writing speed of 69 patients was determined. The patients were divided into groups having normal or abnormal EEG's and normal or abnormal motor mechanisms of writing. Forty-five of the patients were classified according to their reactions in experimental or other situations. The findings and conclusions of this study are:

1. There is hardly any correlation between the two quantities investigated in cases with deviating motor mechanisms of writing or with an abnormal EEG; the correlation is rather high in cases with normal motor mechanisms of writing and normal EEG.

2. This indicates that one or more factors determining the frequency of the alpha rhythm do likewise influence the writing speed. Should an important role be played by other factors this is evidently expressed by deviating motor mechanisms or by an abnormal EEG.

3. The patients were divided into two groups, one writing too slowly with respect to the frequency of their alpha rhythm, the other too fast. This division is related to the reactions of the patients in experimental and other situations.

RÉSUMÉ

La fréquence du rythme alpha et de la vitesse d'écriture fut déterminée chez 69 malades. Les malades étaient divisés en groupes ayant des EEG normaux ou anormaux, et ayant des mécanismes d'écriture normaux ou anormaux. Quarante-cinq des malades étaient classifiés selon leurs réactions vis-à-vis des situations expérimentales ou autres. Les constations et les conclusions de cette étude sont les suivants:

1. Il n'y a pratiquement pas de corrélation entre les deux quantités investigués dans des cas de mécanismes d'écriture déviés ou des EEG anormaux; la corrélation est assez élevée dans des cas avec des mécanismes normaux d'écriture et des EEG normaux.

2. Ceci indique qu'il y a une ou plusieurs facteurs qui déterminent la fréquence du rythme alpha et qui influencent également la vitesse d'écriture. S'il y a d'autres facteurs qui jouent un rôle important ceci se trouvera évidemment exprimé par des mécanismes moteurs déviés ou par un EEG anormal.

3. Les malades étaient divisés en deux groupes, les uns écrivaient trop lentement par rapport à la fréquence de leur rythme alpha, les autres trop rapidement. Cette division a un rapport avec les réactions des malades dans des situations expérimentales ou autres.

ZUSAMMENFASSUNG

Bei 69 Patienten wurde die Frequenz des Alpharhythmus und das Schreibtempo gemessen. Die untersuchten Patienten wurden auf Grund folgender Befunde in Gruppen eingeteilt: Normales oder pathologisches EEG, normale oder abnorme Schreibmotorik. Fünf undvierzig Patienten wurden klassifiziert gemäss der Reaktionen, welche sie in exper-

imentellen oder anderen Situationen aufzeigten.

Die Befunde und Schlussfolgerungen dieser Untersuchung sind wie folgt:

1. Es besteht kaum irgendwelche Beziehung zwischen den zwei untersuchten Quantitäten in Fällen mit abweichender Schreibmotorik oder mit pathologischem EEG. Andererseits ist die Korrelation hoch in Fällen mit normaler Schreibmotorik und normalem EEG.

2. Dies bedeutet, dass ein oder mehrere Faktoren, welche die Frequenz des Alpharhytmus bestimmen, ebenfalls das Schreibtempo beeinflussen. In Fällen, wo eine wichtige Rolle durch andere Faktoren gespielt wird, drückt sich dies klar aus in Abweichungen der Schreibmotorik oder in einem abnormen EEG.

3. Die Patienten wurden in zwei Gruppen eingeteilt, eine, in welcher das Schreiben zu langsam erfolgte in Bezug auf die Frequenz des Alpharhytmus, und eine zweite Gruppe, in welcher das Schreibtempo im Gegenteil zu hoch war. Diese Unterteilung steht in Beziehung mit Reaktionen, welche die Patienten in experimentellen und anderen Situationen zeigten.

We are much indebted to Mr. Ph. van Elteren of the Mathematical Centre in Amsterdam for his help and advice for the statistical preparation of the material and also to Mrs. J. Bastiaans, J. Ladee and J. Thiel for their assistance in classifying the patients according to clinical data.

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DUALITÉ DU SYSTÈME THALAMIQUE DE PROJECTION DIFFUSE

(Antagonisme du système thalamique recrutant et du système réticulaire ascendant) [1]

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Dès la découverte du *système thalamique intralaminaire* (Dempsey et Morison 1942), le problème de sa signification physiologique et de ses corrélations fonctionnelles avec le système réticulaire ascendant de Moruzzi et Magoun (1949) s'est posé.

a) La stimulation des *noyaux intralaminaires* du thalamus à basse fréquence déclenche des réponses « recrutantes » qui présentent une analogie frappante avec les fuseaux d'endormissement (12-15 c/sec.). Ces fuseaux peuvent être encore dérivés des mêmes noyaux après l'ablation du cortex, ce qui prouve leur origine diencéphalique (Dempsey et Morison 1942).

Un stimulus unique appliqué sur ces mêmes structures détermine l'apparition de fuseaux d'endormissement (Hanbery and Jasper 1953). Des injections de pénicilline y entraînent une modification des fuseaux indépendamment de l'interruption ou non du système réticulaire sous-jacent (Hanbery, Ajmone-Marsan et Dilworth 1954). La stimulation à basse fréquence et avec des courants amortis de la partie inférieure de la massa intermedia du thalamus provoque le sommeil chez le chat (Hess 1944); elle induit "des spindles" et "des ondes lentes" dans le cortex (Monnier 1950). Chez le lapin, la stimulation du thalamus médian à basse fréquence, en même temps qu'elle entraîne des réponses recrutantes, tend à tranquilliser l'animal (Monnier et Tissot 1957). Ces faits semblent prouver que le système thalamique à projections diffuses tend à diminuer le degré de vigilance. Mais la stimulation des mêmes noyaux intra-laminaires à fréquence plus élevée donne une réaction d'éveil typique avec activation du comportement et désynchronisation de l'activité électrique du cortex (rythmes rapides de faible voltage) (Hess 1944; Monnier 1950).

b) Le *système réticulaire ascendant* augmente le niveau de vigilance; sa stimulation électrique (Moruzzi et Magoun 1949), humorale (Bonvallet, Dell et Hiebel 1954) ou sensorielle (Gangloff et Monnier 1956) entraîne une activation du comportement avec activité électrique cérébrale d'éveil. Sa stimulation à haute fréquence supprime les réponses recrutantes du thalamus et les fuseaux d'endormissement (Moruzzi et Magoun 1949). La voie ascendante réticulo-corticale est double: d'une part oligo-synaptique par le subthalamus et la capsule interne, d'autre part polysynaptique par le thalamus médian où elle rejoint les structures intra-laminaires (Starzl, Taylor et Magoun 1951).

Ces faits justifient actuellement deux conceptions des corrélations fonctionnelles et structurales des systèmes thalamiques et réticulaires à projections diffuses:

La première conception, *uniciste,* réunit les deux systèmes dans un seul ensemble hiérarchisé de projections diffuses mésodiencéphalo-corticales. L'activation de son pôle inférieur mésencéphalique déterminerait à l'étage sous-cortical et cortical, la réaction d'éveil en même temps qu'elle bloquerait les rythmes lents d'origine diencéphaliques (fuseaux d'endormissement, réponses recrutantes). La désactivation de ce pôle inférieur libérerait au contraire ces composantes diencéphaliques.

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[1] Les résultats de ce travail ont été communiqués à la 52ième Assemblée de la Société suisse de Physiologie, les 17/18 Mai, 1958 à Lausanne.

L'autre hypothèse, *dualiste,* conclut à la coexistence en parallèle de deux systèmes antagonistes intriqués au niveau du thalamus médian. L'étude de l'action topique sur le système nerveux central du lapin de nombreux agents pharmacologiques (chlorpromazine, réserpine, sérotonine, morphine, levorphan et levallorphan; Gangloff et Monnier 1957) a donné des résultats nettement en faveur de cette deuxième hypothèse (Monnier et Gangloff 1956; Monnier 1957).

Nous analyserons d'abord les réponses du cortex à la stimulation du thalamus médian et du système réticulaire. Nous essayerons ensuite de différencier les voies de passage des excitations réticulaires à destination corticale. Enfin, nous fournirons les preuves expérimentales d'un antagonisme fonctionnel entre le thalamus médian et le système réticulaire.

MÉTHODE

Nous avons stimulé chez le lapin, sous anesthésie locale, le thalamus médian et la substance réticulée mésencéphalique. A cette fin, nous avons utilisé un stimulateur de Wyss à impulsions légèrement amorties ou un stimulateur de Grass à impulsions rectangulaires. Nous avons utilisé des impulsions isolées ou de fréquences variables (3-40 c/sec.) d'une durée de 0,4 msec. Les électrodes de stimulation bipolaire sont des aiguilles d'acier du type Hess, isolées sauf à leur extrémité sur 1 mm. et distantes de 1,5 à 3 mm. Simultanément nous avons dérivé l'activité électrique cérébrale à différents niveaux (système réticulé mésencéphalique, thalamus médian, capsule interne et cortex) au moyen de canaux électroencéphalographiques (Schwarzer) couplés à un oscillographe cathodique (Cossor) à deux faisceaux. Les électrodes de dérivation corticale sont en argent et vissées dans la calotte crânienne au contact de la dure-mère. Les électrodes de dérivation subcorticale sont des aiguilles d'argent chloruré ou de platine, isolées sauf à leur extrémité et mises en place grâce au système stéréotaxique de Monnier et Gangloff (1959). Chez un certain nombre d'animaux nous avons détruit la capsule interne et le thalamus au moyen d'une aiguille à pointe mousse selon la technique des lobotomies.

Ce cycle d'expérience a porté sur 31 lapins. Les cerveaux ayant donné les réponses les plus spécifiques ont été examinés histologiquement pour contrôler la position des électrodes et les lésions anatomiques.

RÉSULTATS

1. *Double réponse du cortex à la stimulation du thalamus médian*

La stimulation bipolaire du *thalamus médian* au moyen d'électrodes distantes de 1,5-3 mm. et de chocs isolés de 0,4 msec. avec des voltages variant entre 3 et 10 V. nous a donné sur le cortex deux réponses. La première réponse présente une latence variant entre 6 et 12 msec., avec un maximum d'incidence à 9-10 msec. Bilatérale et généralisée, elle est souvent synchrone sur les deux hémisphères; la réponse contra-latérale peut être toutefois

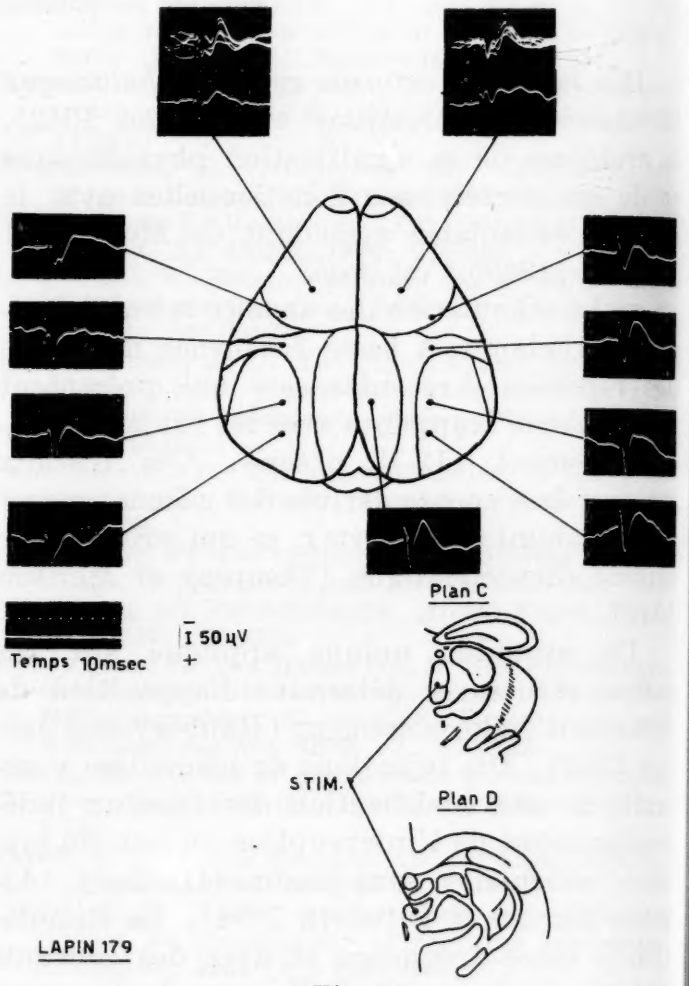


Fig. 1

Réponses corticales bilatérales et généralisées à la stimulation bipolaire du thalamus médian: durée du stimulus (0,4 msec.; dérivations monopolaires). Sur les deux enregistrements supérieurs, une stimulation répétitive 3 c/sec. donne une réponse primaire surface positive (latence 9 msec.) suivie de la réponse secondaire négative, dite « recrutante ». Sur les autres enregistrements la stimulation par choc unique donne aussi une première réponse surface positive, suivie de la deuxième réponse, surface négative.

en retard de 1 à 3 msec. par rapport à la réponse ipsilatérale. Sur les enregistrements monopolaires elle est caractérisée par une déflexion *surface positive* ou à prédominance nettement positive. Lors de la stimulation répétitive à 3 c/sec., cette réponse ne se recrute pas.

La deuxième réponse correspond à la réponse classique recrutante; sa latence varie

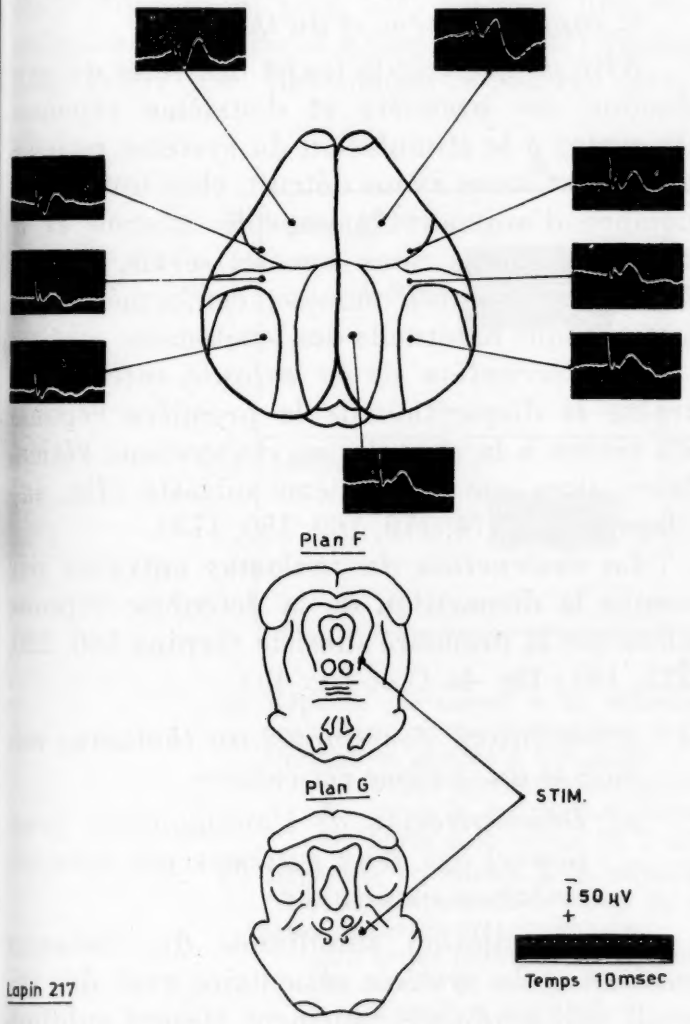


Fig. 2

Double réponse du cortex à la stimulation bipolaire de la substance réticulée mésencéphalique (choc unique; durée 0,4 msec.; 9 V., dérivation monopolaire). Première réponse à prédominance surface négative, latence 6 msec.; deuxième réponse à prédominance surface négative, latence 24 msec.

entre 20 à 36 msec. avec un maximum d'incidence à 28-30 msec. Elle est aussi bilatérale et généralisée, mais prédomine toutefois sur les régions antérieures du cerveau. Parfois parfaitement synchrone, elle est souvent aussi en retard de 3-5 msec. sur l'hémisphère contralatéral. Sur les enregistrements monopolaires, elle présente une forte prédominance *surface négative*. Lors de la stimulation répétitive (3 c/sec.) elle se recrute nettement (augmentation et diminution en 5 à 10 cycles). Le seuil de ces deux réponses n'est pas le même. Pour la stimulation par choc unique, celui de la première est généralement plus bas que celui de la deuxième. Pour la stimulation répétitive, cette différence tend à s'atténuer; souvent même à s'inverser.

La stimulation à des fréquences plus élevées, 30-40 c/sec., tend à faire disparaître la deuxième réponse recrutante alors que la première réponse subsiste (lapins no 168, 148, 163). Il est à noter qu'à cette fréquence on obtient une réaction électrographique d'éveil (arousal reaction) avec une activation du comportement.

2. *Double réponse du cortex à la stimulation du système réticulaire ascendant*

La stimulation bipolaire de la substance réticulée mésencéphalique et pontique au moyen d'électrodes espacées de 3 mm. et d'un choc unique (0,4 msec., 3-12 V.) nous a également donné deux réponses corticales (fig. 2).

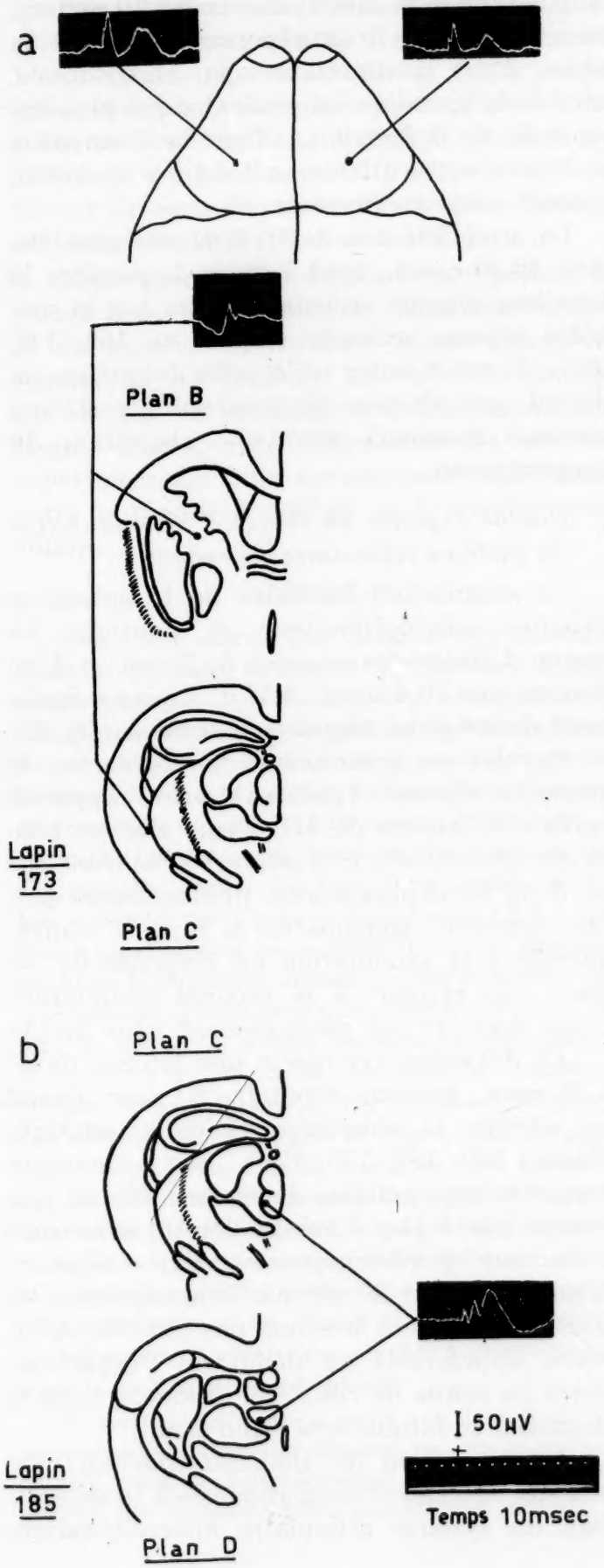
Sur les enregistrements monopolaires, *la première réponse* (pointue) brève apparaît après une latence de 4-7 msec.; elle est bilatérale, généralisée, très souvent synchrone sur les deux hémisphères avec prédominance surface négative. Quelquefois la réponse contralatérale à la stimulation est retardée de 1-2 msec. par rapport à la réponse ipsilatérale. Cette dernière est généralement plus ample.

La deuxième réponse a une latence de 15 à 26 msec., pouvant atteindre 30 msec. quand on stimule la substance réticulée pontique (lapins 185, 182, 175, 176). Sur les enregistrements monopolaires de surface elle est également bilatérale, et habituellement synchrone avec une prédominance surface négative. L'amplitude de la réponse contralatérale est plus faible. Nous n'avons pas noté de différence appréciable au début de l'expérience entre les seuils de ces deux réponses, mais la deuxième se fatigue très rapidement.

La dérivation du thalamus médian nous a donné également deux réponses à la stimulation du système réticulaire mésencéphalique

avec des latences de 5-6 msec. et 12-14 msec. (lapins 176, 185, 22, 229, 214, 224; fig. 3b).

Enfin nous avons obtenu également la première réponse corticale de type réticulé après une latence de 4-5 msec. en stimulant la capsule interne (lapins 176, 163, 173). Nous avons pu dériver par ailleurs de la capsule interne la première réponse à la stimulation de la formation réticulaire pontique après une latence de 5 msec. (fig. 3).



3. *Différentiation des voies de passage des excitations réticulaires par destruction de la capsule interne et du thalamus*

Afin de préciser le trajet des voies de conduction des première et deuxième réponses du cortex à la stimulation du système réticulé ascendant, nous avons détruit, chez un certain nombre d'animaux la capsule interne et le thalamus. Nous nous sommes servis, à cette fin, d'une aiguille mousse, conformément à la technique habituelle des lobotomies.

L'interruption de la capsule interne entraîne la disparition de la première réponse du cortex à la stimulation du système réticulaire, alors que la deuxième subsiste (fig. 4a) (lapins 163, 174, 175, 169, 180, 173).

La destruction du thalamus entraîne par contre la disparition de la deuxième réponse alors que la première subsiste (lapins 180, 220, 215, 191; fig. 4a C et fig. 4b).

4. *Antagonisme fonctionnel du thalamus médian et du système réticulaire*

   a) *Démonstration de l'antagonisme fonctionnel des deux systèmes par leur stimulation simultanée*

La stimulation simultanée du thalamus médian et du système réticulaire avec des stimuli qui, appliqués isolément étaient subliminaires, fait apparaître sur le cortex la première réponse d'origine thalamique (fig. 5A; lapins 217, 209).

Fig. 3

a) Réponse du cortex et de la capsule interne à la stimulation de la substance réticulée pontique (choc unique; durée 0,4 msec.; 9 V.). La dérivation monopolaire des cortex moteurs gauche et droit montre la deuxième réponse après une latence de 30 msec. La dérivation bipolaire de la capsule interne présente une première réponse après une latence de 5 msec. déjà.

b) Double réponse du thalamus médian après 6 et 12 msec. à la stimulation de la substance réticulée mésencéphalique (choc unique; durée 0,4 msec.; 4 V.); dérivation bipolaire).

Si aux réponses corticales obtenues par *stimulation supraliminaire* du thalamus médian seul, on compare les réponses corticales obtenues par stimulation simultanée du thalamus médian avec le même voltage et de la formation réticulée mésencéphalique, on constate que la première réponse thalamique est augmentée alors que la seconde réponse dite recrutante, est diminuée ; c'est le cas aussi bien avec des stimuli isolés (fig. 5B) qu'avec une stimulation répétitive 3 c/sec. (fig. 5C ; lapins 217, 209). Ce phénomène s'observe lors-

b) Démonstration de l'antagonisme fonctionnel des deux systèmes par les variations de la réponse corticale à la stimulation du thalamus médian selon l'état somnolent ou vigile

L'amplitude de la première réponse de courte latence à la stimulation du thalamus médian avec des voltages liminaires varie selon les oscillations somnolence-vigilance de l'activité électrique de base. Elle est de faible amplitude ou absente lorsque le tracé présente des activités lentes (somnolence) ; elle aug-

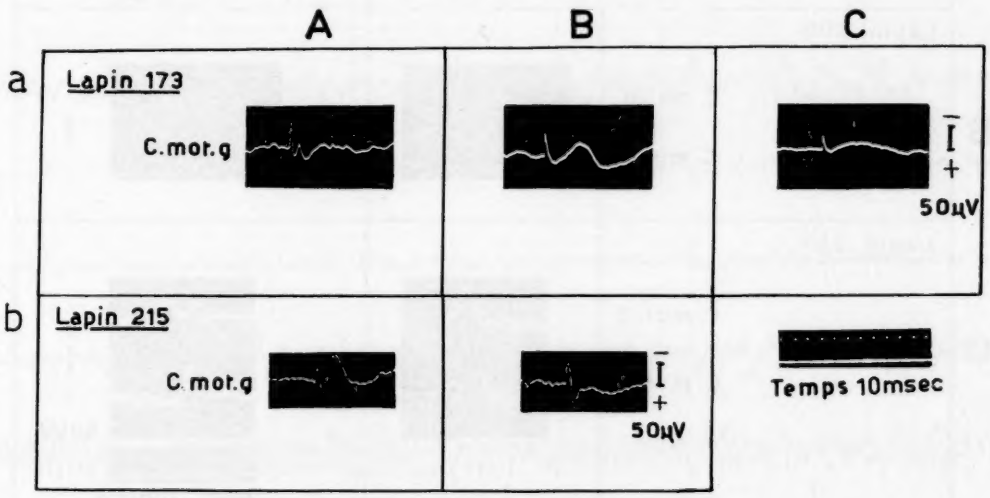


Fig. 4

a) Réponse du cortex à la stimulation de la substance réticulée mésencéphalique après destruction de la capsule interne gauche. Lapin 173: Dérivation corticale bipolaire
A : avant la destruction, première réponse très nette
B : après la destruction, disparition de la première réponse
C : après destruction du thalamus, plus de réponse.

b) Réponses du cortex à la stimulation de la substance réticulée mésencéphalique après destruction du thalamus. Lapin 215: Dérivation bipolaire du cortex moteur gauche
A : avant la destruction, double réponse
B : après la destruction, la première réponse subsiste ; la deuxième réponse a disparu.

que les deux stimuli thalamique et réticulé sont parfaitement synchrones mais aussi lorsque le stimulus réticulé précède le stimulus thalamique de 1-4 msec.

Un stimulus isolé sur le thalamus médian détermine l'apparition sur le cortex d'un « fuseau » d'endormissement. L'application d'un choc unique simultanément sur le thalamus médian et sur la substance réticulée mésencéphalique empêche l'apparition de ce fuseau d'endormissement ou diminue nettement sa longueur et son amplitude (fig. 6 ; lapins 217, 209, 212).

mente nettement lorsqu'il est désynchronisé à la faveur d'un état vigile (fig. 7 ; lapin 217).

c) Démonstration de l'antagonisme fonctionnel des deux systèmes par l'action opposée des drogues ergotropes et tranquillisantes sur la double réponse corticale à la stimulation du thalamus médian

Nous avons examiné l'action de différents agents pharmacologiques à effets ergotropes-vigiles d'une part et somnogènes d'autre part

sur les deux réponses corticales à la stimulation du thalamus médian.

Nous avons constaté que les *drogues « ergotropes »*, qui augmentent l'excitabilité du système réticulaire ascendant accroissent aussi l'amplitude de la première réponse thalamique, tandis qu'elles diminuent plus ou moins celle de la réponse recrutante (fig. 8a), comme l'avaient signalé déjà Gangloff et Monnier [1]

Adrenaline	Lapin nº	220, 217, 208, 209, 212
Dopa	"	" 205, 197, 201, 193, 199
Amphétamine	"	" 209, 206, 208
Levallorphan	"	" 220, 217, 212.

Les *drogues « trophotropes »* tranquillisantes qui diminuent l'excitabilité du système réticulaire ascendant diminuent aussi l'amplitude de la première réponse thalamique, tandis qu'elles augmentent plus ou moins celle de la réponse recrutante secondaire (fig. 8b).

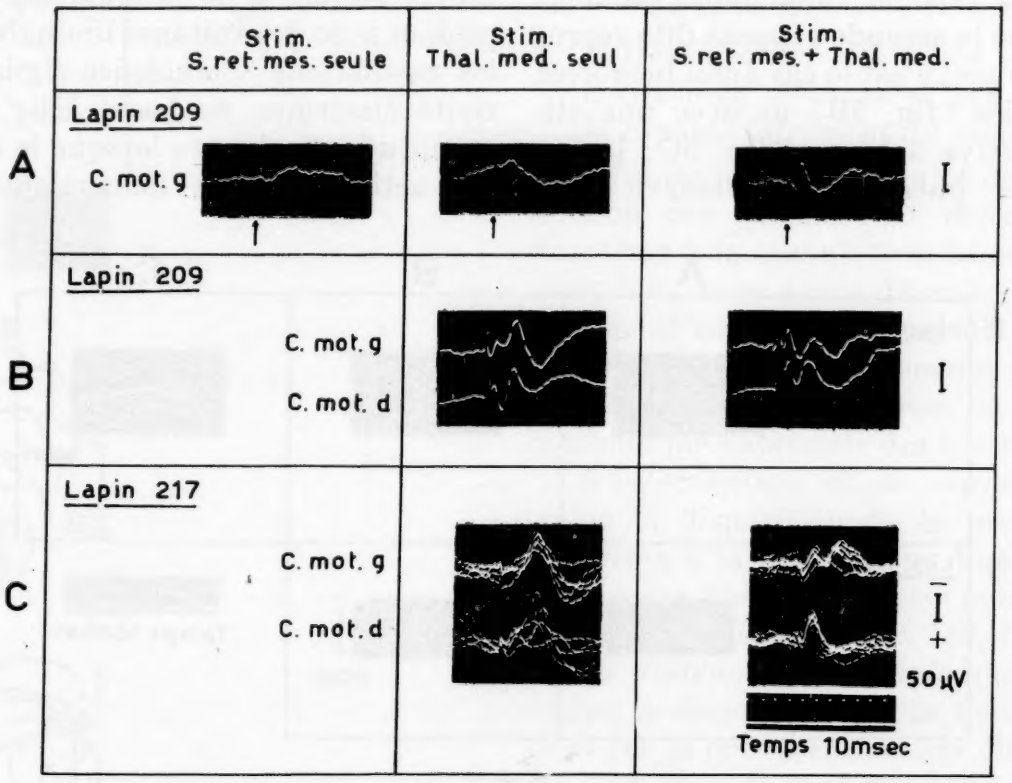


Fig. 5

Stimulation isolée du système réticulaire et du thalamus médian. Stimulation simultanée de la substance réticulée mésencéphalique et du thalamus médian (dérivation corticale bipolaire).

A. *Stimulation subliminaire* du système réticulaire seul: pas de réponse. *Stimulation subliminaire* du thalamus médian seul: pas de réponse. *Stimulation subliminaire* simultanée du système réticulaire mésencéphalique et du thalamus médian: la première réponse thalamique apparaît.

B. La stimulation supraliminaire du thalamus médian seul induit une première réponse petite et une deuxième réponse plus grande. La stimulation simultanée du système réticulaire mésencéphalique et du thalamus médian renforce au contraire la première réponse et diminue la deuxième réponse recrutante.

C. La stimulation répétitive à 3 c/sec. produit les mêmes effets que M.

Chlorpromazine	Lapin nº	170, 168, 163, 180, 193, 205
Réserpine	"	" 222, 229, 214, 224
Morphine	"	" 228, 206, 209, 168.

DISCUSSION

Dempsey et Morison (1942) avaient observé que la stimulation bipolaire du *thalamus médian* chez le chat déclenche une première réponse, apparaissant après 6-12 msec. de latence et précédant la deuxième réponse dite « recrutante ». Ils attribuèrent cette première

[1] Les observations récentes de P. Krupp, M. Monnier et G. Stille montrent que la caféine (25 mg/kg.) diminue également l'amplitude de la réponse recrutante chez le lapin (*Arch. exper. Path.* 1959).

réponse à l'excitation des projections thalamo-corticales spécifiques. Cette interprétation n'est guère plausible, car notre première réponse est à prédominance surface positive, bilatérale et généralisée, alors que la *réponse « augmentante »* spécifique obtenue par stimulation du thalamus latéral est à prédominance *surface négative,* ipsilatérale et localisée (fig. 9).

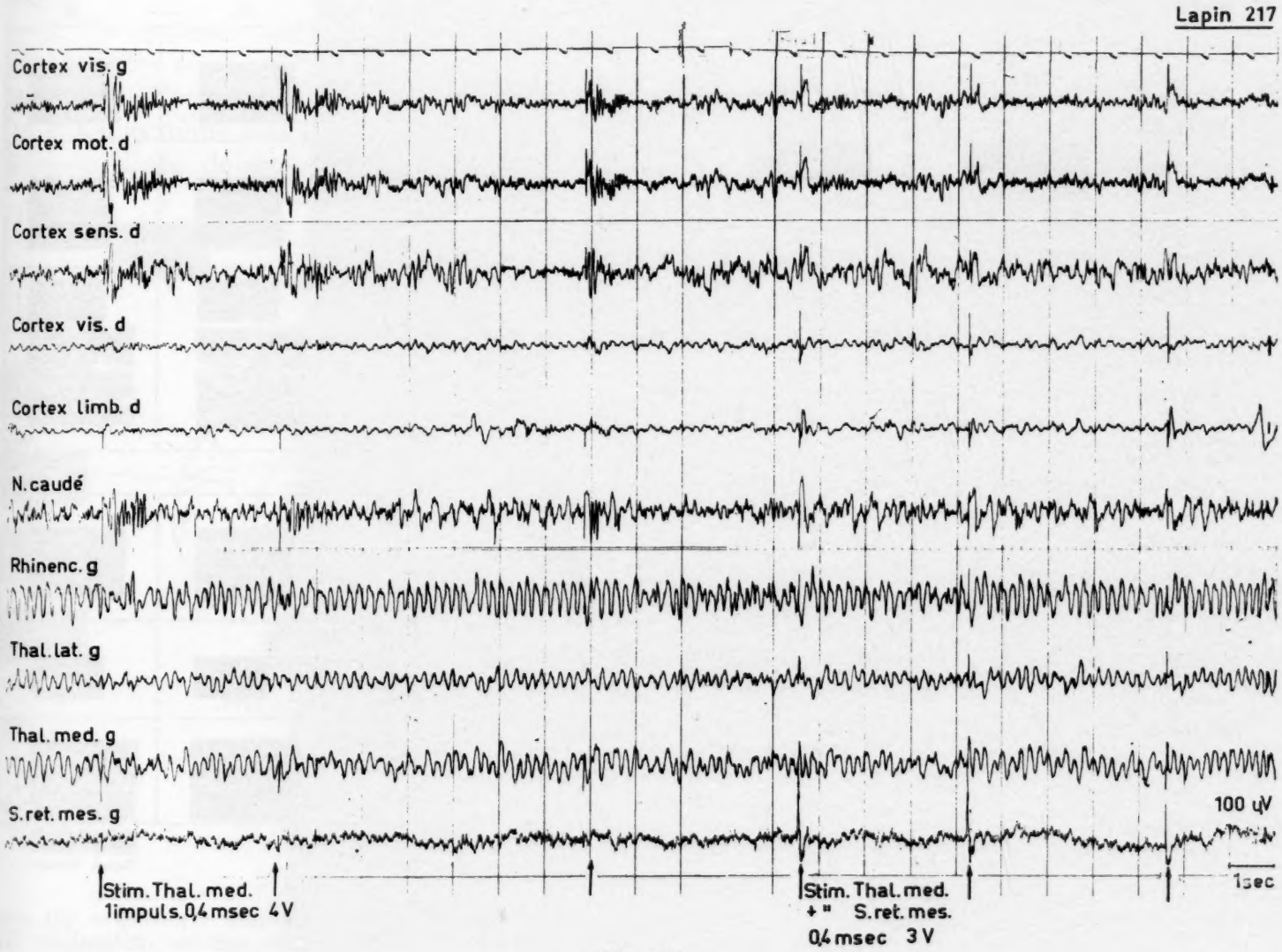


Fig. 6

A gauche, 3 chocs isolés sur le thalamus médian déclanchent des fuseaux d'endormissement. A droite, 3 chocs isolés concomitants sur le thalamus médian et le système réticulaire mésencéphalique ne produisent plus ou presque plus de fuseaux d'endormissement.

Hanbery et Jasper (1953), Verzeano, Lindsley et Magoun (1953) ont décrit simultanément lors de la stimulation bipolaire du noyau ventral antérieur du thalamus chez le chat et le singe, une réponse de 6-12 msec. de latence. Nos résultats chez le lapin sont en accord avec ceux de ces auteurs. Jasper indique comme latence la plus fréquente 10 msec., ce que nous retrouvons également. Magoun note la prédominance surface positive que nous obtenons aussi. Contrairement à Jasper, il indique que cette réponse est « recrutante ». Comme ce dernier auteur, nous n'avons pas observé sur nos enregistrements de recrutement.

Magoun attribue cette réponse à courte latence à l'excitation d'une voie oligosynaptique du système de projection diffuse du thalamus, par opposition à la réponse dite recrutante, classique qui traduit l'excitation d'une chaîne polysynaptique. Dans cette conception les deux réponses appartiennent donc au même système. Jasper soulève par contre l'hypo-

thèse suivante : « The diffuse short latency responses represent a separate system, at least in part, perhaps containing « fibres de passage » from extrathalamic sources (basal diencephalon or midbrain) ». Nos résultats appuient très fortement cette dernière hypothèse. Ils suggèrent même que *la réponse à courte latence appartient au système réticulé.* En

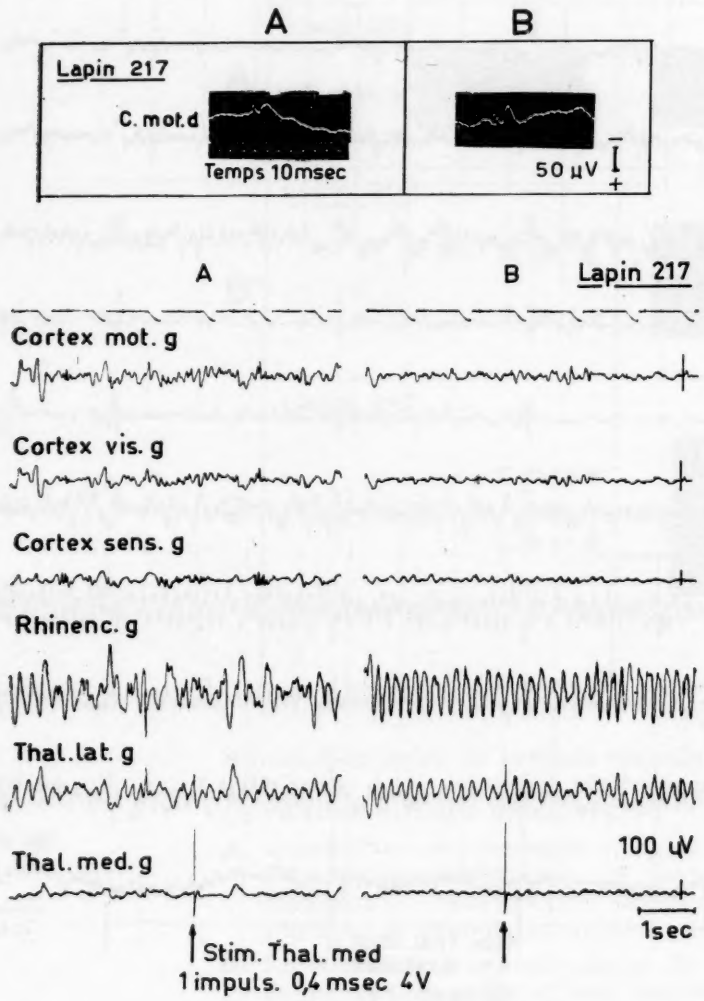


Fig. 7

Variations d'amplitude de la première réponse thalamique avec les fluctuations de l'activité électrique spontanée selon le degré de somnolence ou de vigilance. Stimulation liminaire du thalamus médian. Dérivation corticale bipolaire;

A : animal somnolent; la première réponse thalamique est très petite;

B : animal réveillé par un coup de sifflet; la première réponse thalamique est nettement plus grande.

effet, nous constatons que la réponse thalamique de courte latence augmente lors de la stimulation simultanée du thalamus et de la substance réticulée mésencéphalique alors que la réponse recrutante diminue.

L'amplitude de la réponse thalamique de courte latence obtenue avec des stimuli liminaires varie avec les oscillations de l'activité électrique de base. Elle est plus grande lorsque le tracé présente une activité d'éveil, plus petite lorsqu'il présente des activités lentes de somnolence.

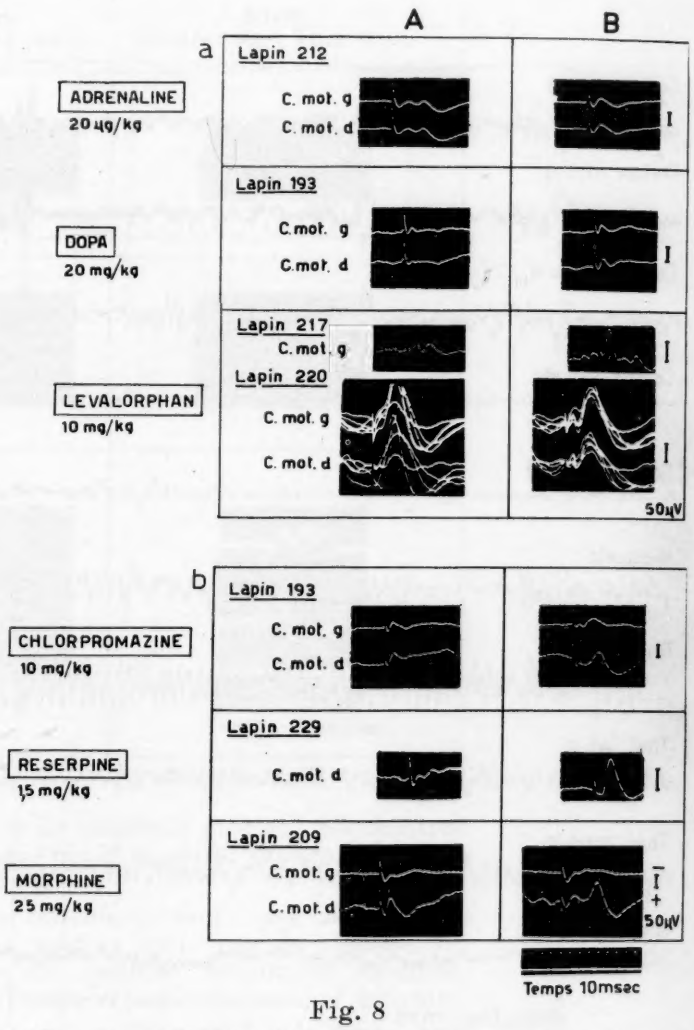


Fig. 8

a) Les agents pharmacologiques ergotropes qui augmentent l'excitabilité du système réticulaire ascendant, accroissent aussi la première réponse corticale à la stimulation du thalamus médian et dans la plupart des cas diminuent la deuxième réponse dite « recrutante ».

b) Les agents pharmacologiques qui modèrent l'excitabilité du système réticulaire ascendant diminuent aussi la première réponse thalamique et augmentent la deuxième réponse thalamique dite recrutante.

A : avant la drogue

B : après la drogue

Les drogues qui augmentent les réponses de la substance réticulée mésencéphalique augmentent également la réponse thalamique de courte latence; les drogues qui diminuent au contraire les réponses de la substance réticulée

mésencéphalique diminuent la réponse thalamique de courte latence, tandis qu'elles augmentent plus ou moins la réponse recrutante.

En conclusion, ces résultats nous amènent à postuler l'existence de *deux systèmes antagonistes de projections diffuses, régulateurs de l'activité électrique cérébrale* et de l'état vigile :

1. Un système thalamique et polysynaptique, dont les voies ont été bien précisées par les travaux de l'école de Jasper (1956).

2. Un système réticulé ascendant à voie réticuo-corticale double : l'une oligosynaptique

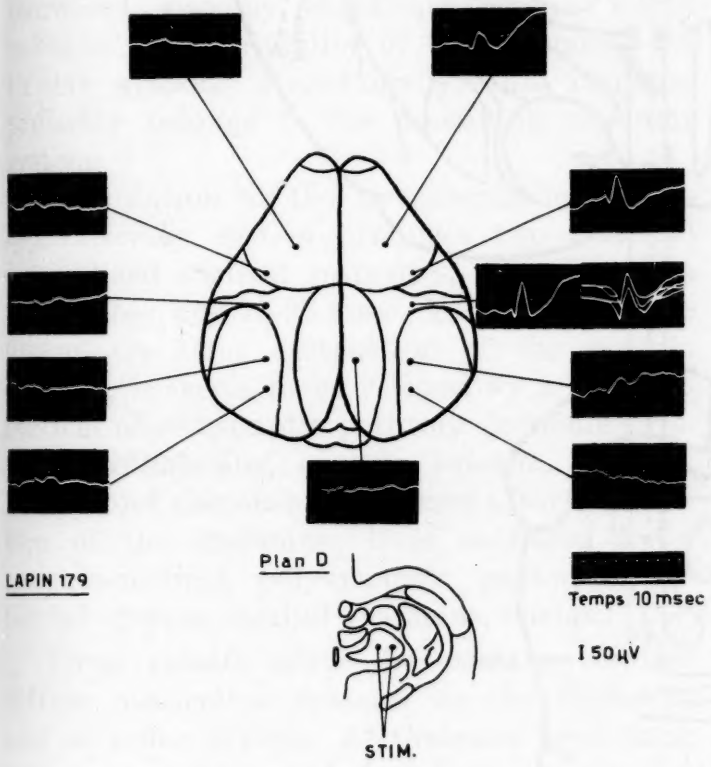


Fig. 9

La stimulation du thalamus ventro-latéral induit une réponse corticale ipsilatérale et surface négative, caractéristique des projections thalamo-corticales spécifiques par opposition aux projections diffuses.

par le subthalamus et la capsule interne, l'autre polysynaptique par le thalamus médian où elle est fortement intriquée avec le système recrutant.

La notion d'une conduction oligosynaptique rapide et d'une conduction polysynaptique plus lente à l'intérieur du système réticulaire s'accorde assez bien avec les données anatomiques récentes qui mettent en évidence dans la substance réticulée des neurones à axones courts et des neurones à axones longs (Brodal 1957 ; Papez 1956) (fig. 10). L'équilibre de ces deux systèmes joue vraisemblablement un rôle primordial dans la détermination du niveau de vigilance.

A la lumière de notre interprétation dualiste on conçoit que la stimulation du thalamus à basse fréquence avec des stimuli de longue durée excitent plus électivement le système recrutant et tranquillise l'animal ou même l'endorme (Hess 1944 ; Monnier 1950). Au contraire, la stimulation à plus haute fréquence (30-200 msec.) avec des stimuli de courte durée excite électivement le système réticulé activateur dans son trajet thalamique et produit une réaction d'éveil. On comprend ainsi la difficulté de reproduire les expériences de Hess sur le sommeil, car on stimule toujours au niveau du thalamus médian les deux systèmes à la fois.

RÉSUMÉ

La *stimulation du thalamus médian* induit chez le lapin, en plus de la réponse recrutante classique, une première réponse corticale, surface positive, de courte latence (6-12 msec.), bilatérale, généralisée et ne recrutant pas. Cette réponse subsiste lors de la stimulation à des fréquences de 30 à 40 c/sec., qui produit une réaction d'éveil. Son amplitude augmente avec la vigilance et diminue avec la somnolence. Elle est augmentée par la stimulation concomitante du thalamus médian et de la substance réticulée mésencéphalique. Elle est augmentée enfin par les drogues ergotropes qui augmentent l'excitabilité du système réticulaire ascendant. Fonctionnellement elle appartient donc vraisemblablement au système réticulaire ascendant.

La *stimulation du système réticulé mésencéphalique* provoque deux réponses corticales bilatérales généralisées après des latences de 4-7 msec. et 15 à 26 msec. La première réponse disparaît après destruction de la capsule interne ; elle paraît transmise par une voie réticulo-corticale oligo-synaptique (système réticulé, subthalamus, capsule interne, cortex). La deuxième réponse disparaît après destruction du thalamus ; elle traduit l'excitation d'une voie réticulo-corticale polysynap-

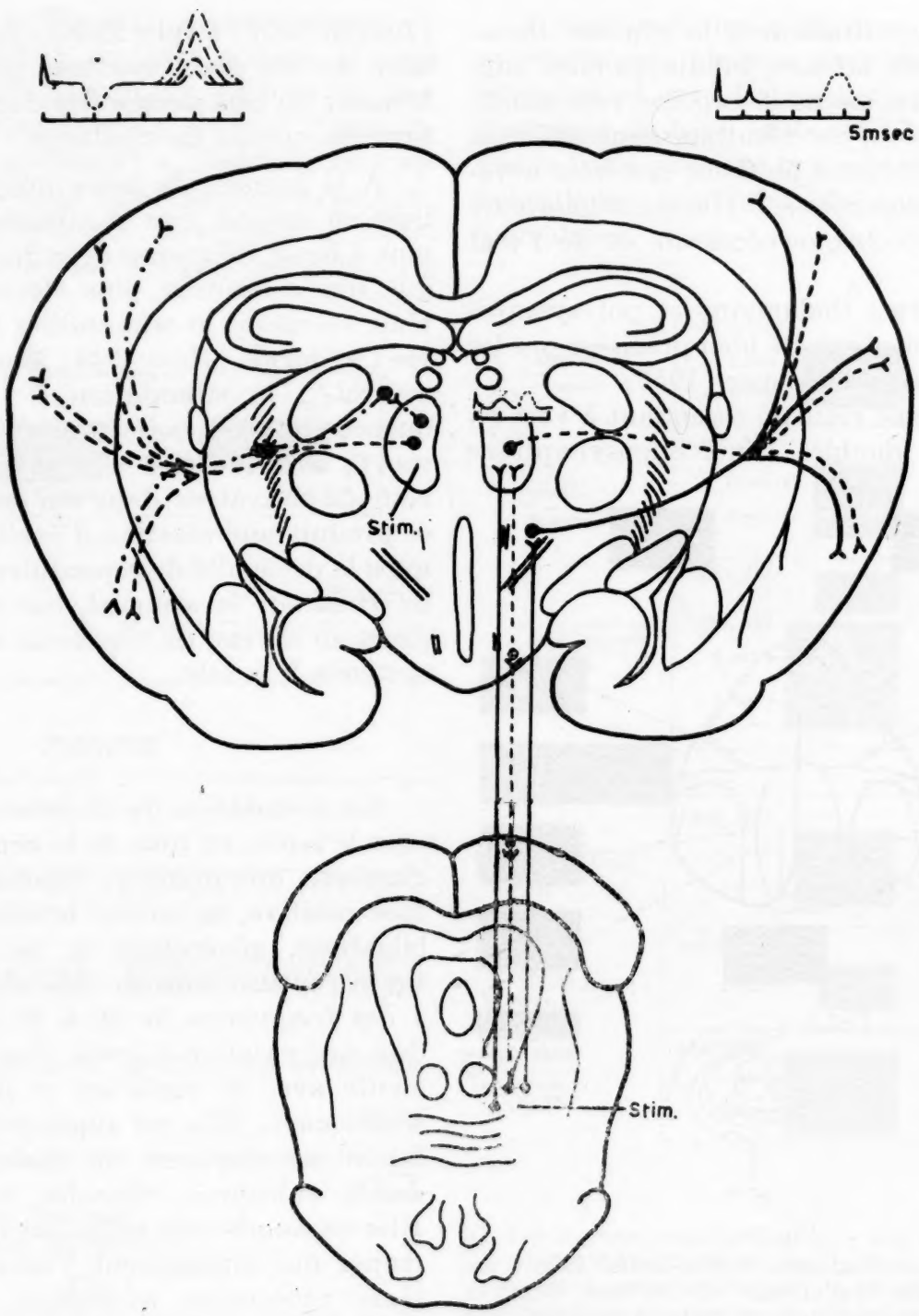


Fig. 10

Diagramme illustrant la dualité des systèmes de projection diffuse du thalamus médian:

à droite: - - - - - - voie réticulo-corticale polysynaptique par le thalamus médian;
——— voie oligosynaptique par le subthalamus et la capsule interne;
à gauche: - - - - - - voie de la première réponse corticale à la stimulation thalamique;
—.—.— voie de la deuxième réponse corticale recrutante.

tique (système réticulé, thalamus médian, cortex).

Ces résultats parlent en faveur de l'existence de deux systèmes de projections diffuses thalamique et réticulaire. A partir du thalamus médian ces systèmes sont intriqués mais ils restent distincts. Leur antagonisme réciproque joue vraisemblablement un rôle important dans la régulation de la vigilance et de la conscience.

SUMMARY

Stimulation of the *medial thalamus* induces in the cortex of the rabbit, beside the classical recruiting response, a first cortical response, surface positive, of short latency (6-12 msec.), bilateral, generalized and non recruiting. This response persists during stimulation at frequencies from 30 to 40 c/sec., which produce an arousal reaction. Its amplitude increases with wakefulness and decreases with sleepiness. It is increased by concomitant stimulation of medial thalamus and mesencephalic reticular formation. It is increased also by ergotropic drugs, which enhance the excitability of the ascending reticular system. Functionally, this response probably belongs to the ascending reticular system.

Stimulation of the mesencephalic *ascending reticular system* produces two bilateral generalized cortical responses, after latencies of 4-7 msec. and 15-26 msec. The first response disappears after destruction of the capsula interna; it seems to be relayed by a reticulo-cortical oligo-synaptic pathway (reticular system, subthalamus, capsula interna, cortex). The second response disappears after destruction of the thalamus; it is mediated by a reticulo-cortical polysynaptic pathway (reticular system, medial thalamus, cortex).

These results prove the existence of two diffuse projection systems in the thalamus and reticular system. At thalamic level these systems are intricated, but they remain distinct. Their reciprocal functional antagonism probably plays an important role in the regulation of wakefulness and consciousness.

ZUSAMMENFASSUNG

Neben der klassischen rekrutierenden Antwort ergibt die *Reizung des medianen Thalamus* beim Kaninchen eine erste corticale, oberflächenpositive Antwort von kurzer Latenz (6-12 msec.), die bilateral und generalisiert auftritt und nicht rekrutiert. Diese Antwort bleibt bei Reizung mit Frequenzen von 30-40 c/sec., die eine Wachreaktion auslösen, bestehen. Ihre Amplitude nimmt im Wachzustand zu und ist bei Schläfrigkeit vermindert. Sie wird ebenfalls durch gleichzeitige Reizung des medianen Thalamus und der Substantia reticularis mesencephalica vergrössert. Endlich zeigt sich auch eine Amplitudenzunahme nach ergotropen Pharmaca, welche die Erregbarkeit des aufsteigenden Reticularissystems erhöhen. In funktioneller Hinsicht gehört sie somit sehr wahrscheinlich zum aufsteigenden Reticularissystem.

Die *Reizung des mesencephalen reticulären Systemes* ergibt zwei bilaterale, generalisierte, corticale Antworten nach Latenzen von 4-7 msec. und 15-26 msec. Die erste Antwort verschwindet nach Zerstörung der Capsula interna; sie scheint durch eine oligosynaptische, reticulo-corticale Bahn (Reticularissystem, Subthalamus, Capsula interna, Cortex) weitergeleitet zu werden. Die zweite Antwort bleibt nach Zerstörung des Thalamus aus; sie resultiert aus der Reizung einer polysynaptischen, reticulo-corticalen Bahn (reticuläres System, medianer Thalamus, Cortex).

Diese Resultate sprechen für das Vorhandensein zweier diffuser Projektionssysteme, eines thalamischen und eines reticulären. Vom medianen Thalamus an sind diese Systeme einander genähert, bleiben jedoch deutlich unterscheidbar. Ihr reziproker Antagonismus ist wahrscheinlich von hervorragender Bedeutung für die Regulation von Wachzustand und Bewusstsein.

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STUDIES ON THE DIPHASIC WAVE FORM OF THE GALVANIC SKIN REFLEX

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The galvanic skin reflex, abbreviated "GSR", has been recorded by two methods: "current method" (Veraguth) and "potential method" (Tarchanoff). In the former, the GSR in man is ordinarily characterized by a monophasic deflection, while in the latter, the GSR not only sometimes has a monophasic deflection, but also at times a diphasic deflection (Darrow 1927; Darrow *et al.* 1957; Fujimori 1955, 1956; Gildemeister 1923; Nakayama and Takagi 1958).

Using DC amplifier and preventing wave form distortion by electric current in the measuring circuit and by the activity at the skin under an indifferent electrode, Fujimori (1955, 1956) showed that the diphasic potential GSR curve might be due to the activity at a single limited skin area of the palm. Furthermore, Fujimori (1955, 1956) and Yokota (1957 a and b) noticed that local cooling, local exsanguination and pressing one side of the chest changed the diphasic potential GSR curve to a monophasic one, while at the control area, it remained still diphasic. Recently, Nakayama and Takagi (1958) obtained the same results after having re-examined these experiments.

In the present study, further experiments have been made to elucidate mechanisms underlying the appearance of the diphasic potential GSR curve in man by changing room temperature and local skin temperature.

METHODS

Experiments were conducted in winter on 27 healthy male adults ranging in age from 19 to 34 years. During the experiments, they were comfortably sitting at rest.

Small amalgamated zinc discs (5 mm. in diameter) were attached to the skin with a paste made of kaoline and saturated zinc sulphate solution; the different electrode to the palm or the dorsum of hand and the indifferent electrode to the volar aspect of forearm. The skin under the indifferent electrode was anesthetized by subcutaneous injection of 0.5 per cent novocaine solution (adrenalin added) in order to inactivate the area during the experiment. It was verified by use of a galvanometer (10^{-8}A) before each experiment that there existed no recognizable electric current in the input circuit.

The GSR was recorded, in most cases by a two channel and in some cases by a six channel amplifier and inkwriting oscillograph (electroencephalograph) with the time constant adjusted to infinity or to 3.0 seconds. The grid current of the amplifier was within 10^{-8}A.

For eliciting the GSR, a series of stimulations: sudden coughing, pricking, hand clapping noise and faradic stimulation, were used.

Localized warming of a hand was effected by keeping it in a box heated with a 200 Watt lamp. Skin temperature of the active skin area was measured with a thermister thermometer.

Room temperature was raised step by step from 15 to 20, 25, 30, 35 and 40°C. At each temperature, the GSR was recorded after the skin temperature had reached an equilibrium at which it remained approximately constant, namely, about 20 min. after the room temperature had reached the expected degrees.

RESULTS

I. Wave form distortion of the potential GSR curve due to the CR amplification and general characteristics of the potential GSR curve.

As preliminary experiments, simultaneous recording of potential GSR curves from the same electrodes was conducted using six channel amplifier with various time constants: infinity, 3.0, 1.5, 0.2 and 0.5 sec., in order to elucidate wave form distortion due to CR amplification of different time constants.

As a result, it was found that CR amplification with time constant of 3.0 sec. was applicable instead of DC amplification at ordinary room temperature, allowing a slight wave form distortion (fig. 1). In the present experiments, therefore, CR amplification with time constant of 3.0 sec. was used in most experiments for practical convenience.

In the present experiment, the wave form of the potential GSR curve was classified into four types: type *a* (monophasic), type *b* (with positive deflection within base line), type *c* (diphasic, but smaller positive than negative deflection) and type *d* (diphasic, with larger positive than negative deflection) (fig. 2).

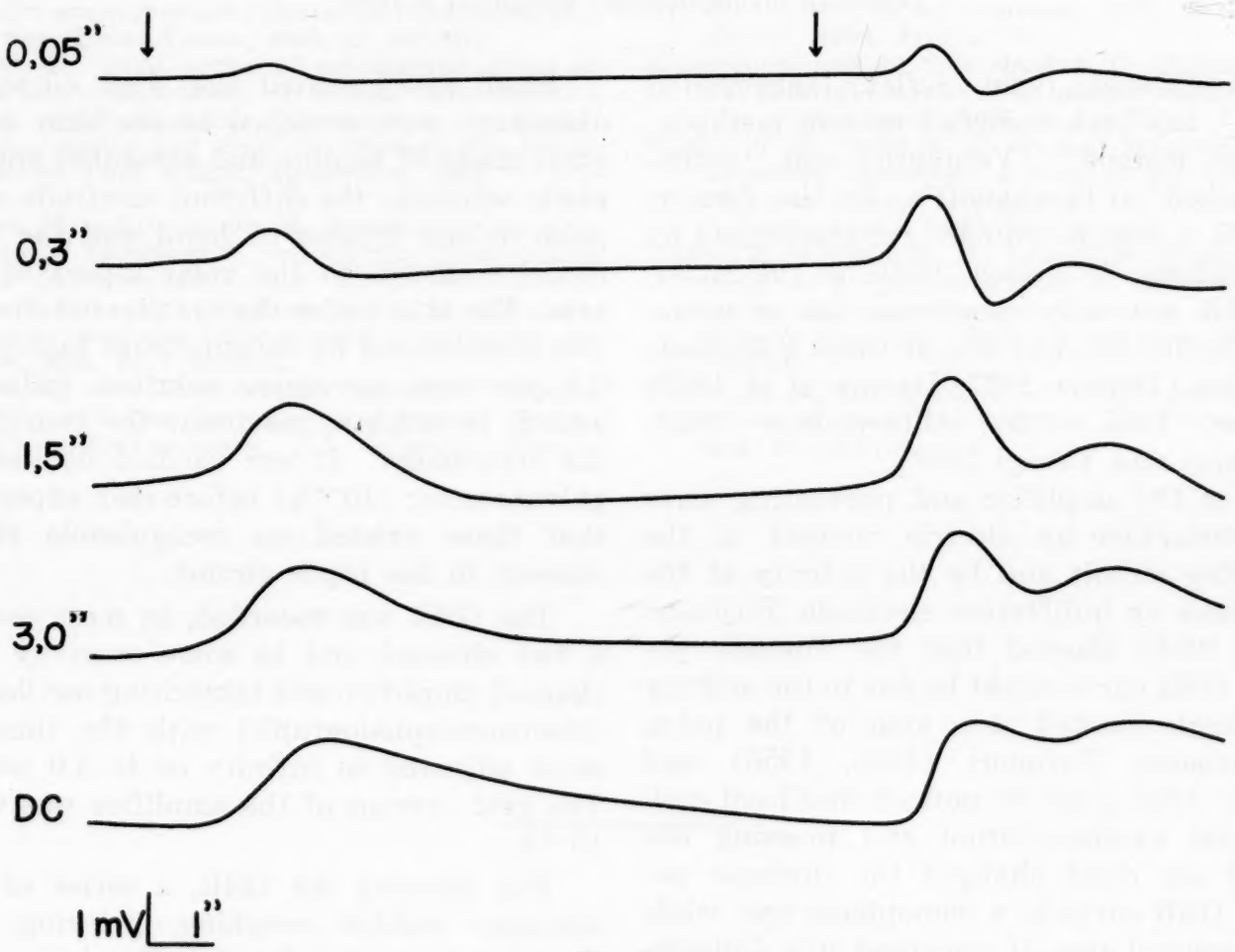

Fig. 1

Wave form distortion of the potential GSR curve due to CR amplification.
Potential GSR curves were simultaneously recorded from the same electrodes by means of amplifiers with different time constants.
Time constant of each amplifier is shown in the left column. Wave form distortion became markedly distinct with the decrease of time constant: slight positive deflection in the second wave recorded by the DC amplifier grew deeper and deeper until at last it extended below the base line.

With regard to general characteristics of the potential GSR curve, the following results were also obtained in the preliminary experiment:

(1) In general, the stronger the applied

faradic stimuli, the more easily the diphasic curve with deeper positive deflection was caused to appear.

(2) The GSR curve changed frequently to diphasic from monophasic following repeated stimulations, but it became monophasic again after a few minutes' pause.

(3) When the GSR of the potential method was recorded simultaneously with the GSR of the current method from different parts of the same palm, diphasic potential changes usually corresponded to larger resistance changes.

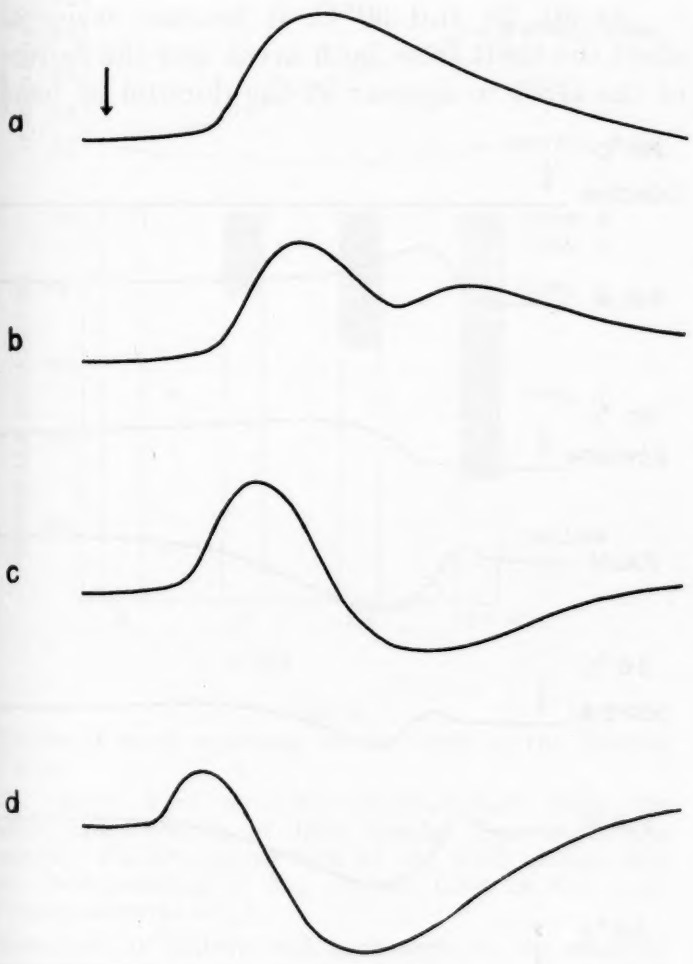

Fig. 2

Schemas illustrating the different types of the potential GSR curve.
a: monophasic;
b: with positive deflection within base line;
c: diphasic, but with smaller positive than negative deflection;
d: diphasic, with larger positive than negative deflection.

II. Effects of room temperature on the potential GSR.

The potential GSR curve at both the palm and the dorsum of hand were recorded simultaneously and effects of room temperature upon those curves were investigated on 17 subjects.

Following the rise of room temperature, skin temperature rose gradually at both the palm and the dorsum of hand, but the GSR at the two areas changed differently both in latency and in wave form.

(1) Latency: At both the palm and the dorsum of hand, the latency of the GSR shortened with the rise of room temperature. It was noticeable that the latency of the GSR at the dorsum was always longer than that of the corresponding GSR at the palm when the room temperature was below 25°C. In most cases, the skin temperature at the dorsum of hand was lower (by 0.1-3.1°C) than at the palm in this experiment. However, even in two cases where the skin temperature of the dorsum of hand was higher respectively by 1.8 and 2.3°C than that of the palm, the latency at the dorsum was longer than that at the other area. When the room temperature was above 30°C, however, no significant difference of the latency between these two areas was recognized.

TABLE I

The percentage of each type of the GSR curve at different room temperatures.

		ROOM TEMPERATURE (°C)					
		15	20	25	30	35	40
PALM	Failure	0	0	0	0	6.4	9.2
	Type *a*	53.8	16.0	12.4	7.3	50.6	55.3
	Type *b*	6.6	11.2	13.3	19.3	17.3	18.4
	Type *c*	15.1	22.6	25.3	21.1	16.4	8.9
	Type *d*	24.5	50.0	49.0	52.8	9.2	8.2
DORSUM OF HAND	Failure	67.0	35.9	21.2	4.2	0.6	0
	Type *a*	27.3	28.0	28.9	13.2	0	1.4
	Type *b*	2.3	17.2	20.5	13.3	1.3	1.7
	Type *c*	2.6	11.5	5.5	14.3	10.3	1.6
	Type *d*	0.8	7.5	23.9	54.8	87.8	95.2

GSR curves were recorded from the palm and the dorsum of hand simultaneously. This result was obtained from 170 GSRs of 17 men at each temperature. Percentages of four types and of failure at each temperature are shown. Failure means the case where the corresponding GSR by the same stimulation was recognized either at the palm or at the dorsum of hand. (For details see text.)

(2) Wave form: Characteristic differences of the wave form of the GSR were observed between the palm and the dorsum of hand during the course of raising room temperature (table I, fig. 3).

At 15°C, the GSR could be elicited from the palm in all subjects when strong stimuli were applied, but it was not always so at the dorsum of hand. Five subjects did not show any GSR at the dorsum and the other 12 showed the GSR at the dorsum less frequently than at the palm. That is to say, at the dorsum of hand, the GSR corresponding to that at the palm, failed to appear in 67.0 per cent. At this room temperature, the wave form of the GSR was frequently monophasic at both the palm (53.8 per cent) and the dorsum of hand (82.9 per cent of appeared GSR).

At 20, 25 and 30°C, it became easier to elicit the GSR from both areas and the failure of the GSR to appear at the dorsum of hand

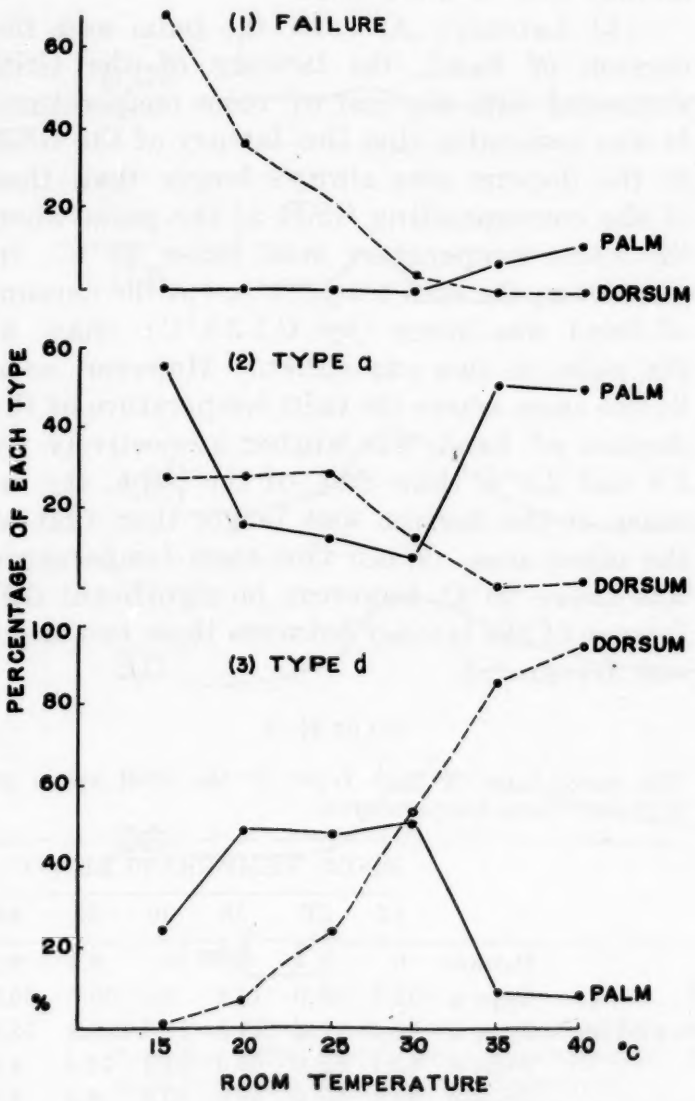

Fig. 3

Differences between the GSR at the palm and that at the dorsum of hand at different room temperatures.

(1) At the dorsum, the GSR frequently fails to appear at lower room temperature and the percentage of failure decreases gradually with the rise of room temperature, while at the palm, the situation is reverse.

(2) (3) At the dorsum type *a* decreases and type *d* increases markedly at higher room temperature, while at the palm, type *a* appears in high percentage at both higher and lower room temperatures and at higher room temperature, type *d* decreases significantly.

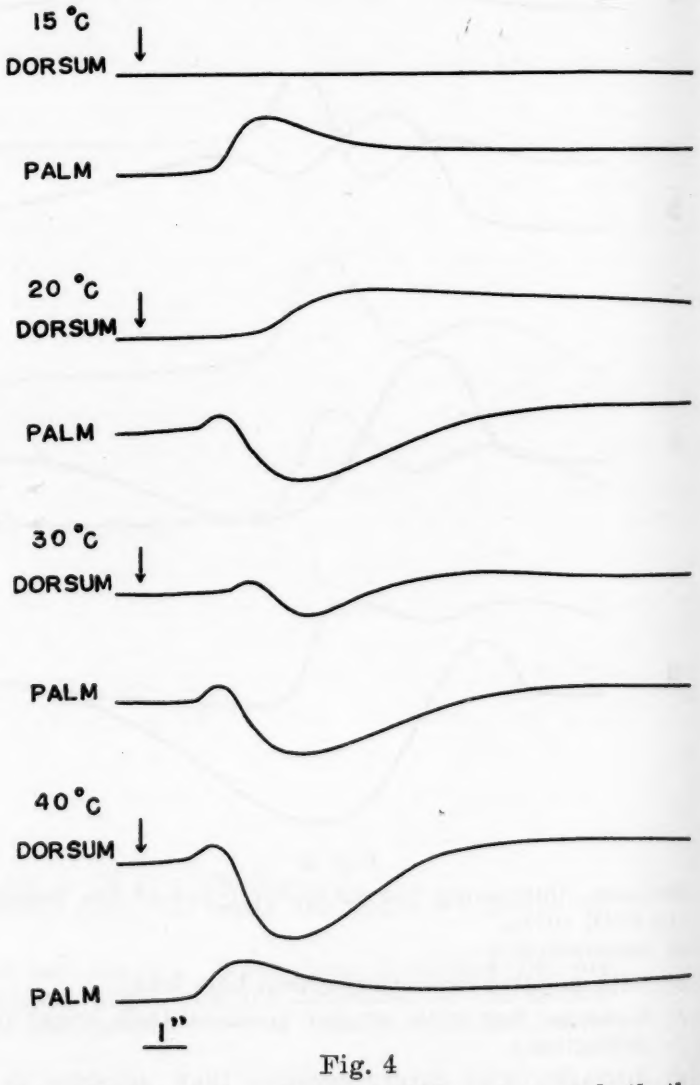

Fig. 4

Wave form of the potential GSR curve at both the palm and the dorsum of hand at different room temperatures.

The GSR was recorded from the palm and the dorsum of hand simultaneously at different room temperatures.

At 15°C., type *a* appeared at the palm and no GSR was recognized at the dorsum of hand. With the rise of room temperature, the wave form shifted from type *a* to type *d* at both areas. However, at 40°C., the GSR at the palm became type *a* again.

decreased in percentage with the rise of room temperature (35.9, 21.2 and 4.2 per cent at 20, 25 and 30°C, respectively). As to the wave form, with the rise of room temperature, type *a* decreased and advanced types especially type *d* increased in percentage at the palm (type *a*: from 53.8 to 7.3 per cent, type *d*: from 24.5 to 52.8 per cent) as well as at the dorsum of hand (type *a*: from 27.3 to 13.2 per cent, type *d*: from 0.8 to 54.8 per cent). However, type *d* was more frequently recognized at the palm than at the dorsum until 25°C. In other words, the GSR of type *d* appeared at the palm in company with the GSR of the other types at the dorsum.

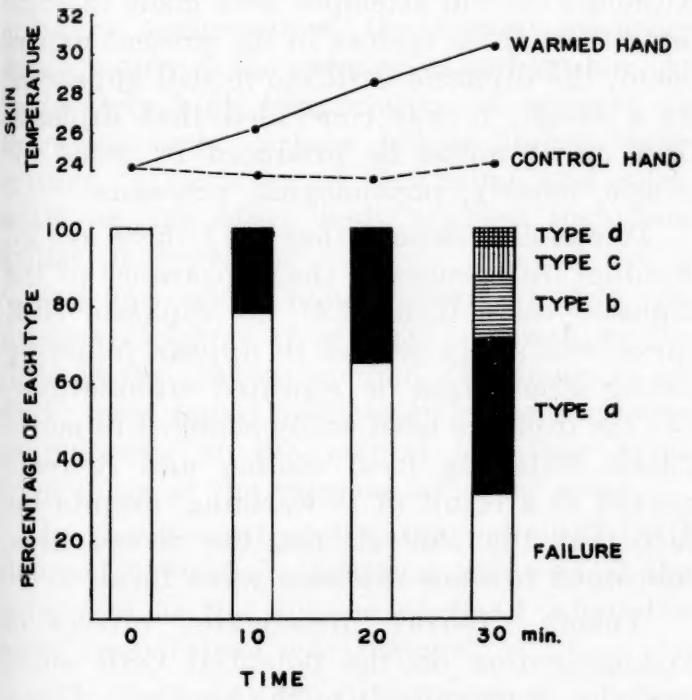

Fig. 5

Effects of local warming on the GSR at the dorsum of hand.

GSR curves were recorded simultaneously from the palms and dorsums of both hands. One hand was warmed. Failure means lack of the GSR at the dorsum corresponding to the obvious GSR at the palm of the ipsilateral hand.

Percentage of failure and each type at the warmed dorsum corresponding to the failure at the control dorsum are shown. With the rise of the skin temperature of the warmed hand, failure decreases gradually and advanced types appear at the warmed dorsum. The percentage of failure at the control dorsum were 41.6 per cent before and 58.1 per cent after 30 min.

At 35 and 40°C, however, the situation as to the two areas reversed. The GSR appeared less frequently at the palm than at the dorsum; the GSR at the palm corresponding to that at the dorsum of hand failed to appear not so rarely (6.4 and 9.2 per cent, at 35 and 40°C respectively), and at the palm, the wave form of the GSR was frequently of type *a* (50.6 and 55.3 per cent, at 35 and 40°C respectively) while at the dorsum that was almost always of type *d* (87.8 and 95.2 per cent at 35 and 40°C respectively). Namely, type *a* was frequently recognized both at low room temperature and at higher room temperature at the palm.

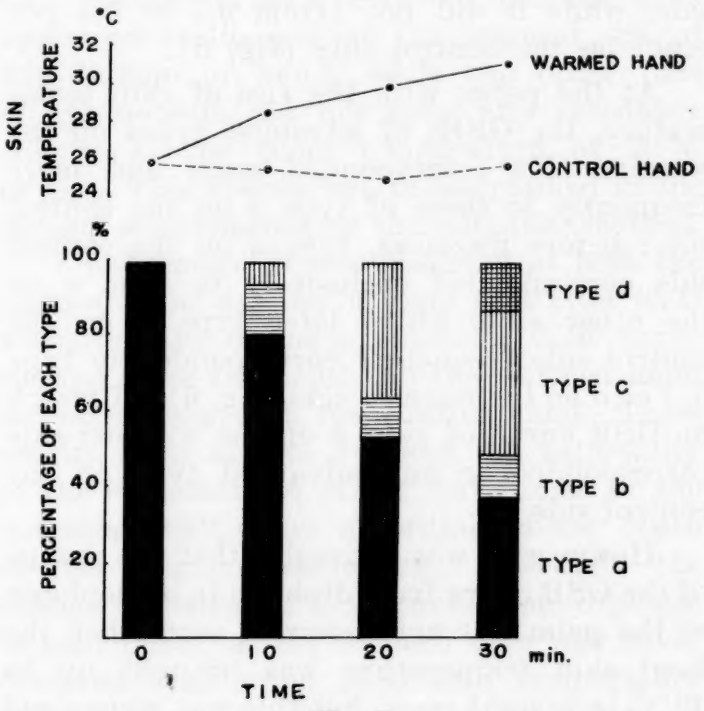

Fig. 6

Effects of local warming on the GSR at the palm. GSR curves were recorded simultaneously from the palms and dorsums of both hands. One hand was warmed. The percentage of each type on the control side corresponding to type *a* on the control side are shown at each 10 min. after the warming. With the rise of skin temperature, advanced types appear and increase in percentage on the warmed side.

III. Effects of local warming upon the potential GSR curve.

In order to elucidate direct effects of local warming upon the wave form of the GSR, further experiments were conducted on 10 subjects at the room temperature of 20-25°C, warming one hand. GSR curves were simultaneously recorded from the palms and the dorsums of both hands, using 6 channel electroencephalograph.

At the warmed hand, the latency of the GSR markedly shortened with the rise of skin temperature at both the palm and the dorsum.

At the dorsum, it became easier to cause the GSR to appear on the warmed side: the percentage of failure of the GSR corresponding to that of the palm decreased (from 41.6 to 25.2 per cent) on the warmed side, while it did not (from 41.6 to 58.1 per cent) on the control side. In addition, with the rise of skin temperature, type *d* increased in percentage (from 5.7 to 16.3 per cent) on the warmed side, while it did not (from 5.7 to 3.5 per cent) on the control side (fig. 5).

At the palm, with the rise of skin temperature, the GSRs of advanced types on the warmed side corresponded more and more frequently to those of type *a* on the control side: before warming, type *a* on the control side corresponded exclusively to type *a* on the other side, while, later type *a* on the control side frequently corresponded to type *b*, *c* or *d* on the warmed side (fig. 6); although no GSR curve of type *a* on the warmed side corresponded to any advanced type on the control side.

However, it was noticeable that the change of the GSR curve from diphasic to monophasic at the palm was not observed, even when the local skin temperature was brought up to 40°C in several cases, but this was recognized at higher room temperature.

DISCUSSION

1. General characteristics of the potential GSR curve and its wave form.

The GSR has been recorded by two methods: "current method" (Veraguth) and "potential method" (Tarchanoff). In the employment of the former, many attempts have been unsuccessfully made to express the reflex activity quantitatively. In the latter, the amplitude of the GSR may be measurable quantitatively in mV. or μV. unit, but the wave form of the GSR frequently becomes diphasic, and thus difficulties are still involved in its quantitative expression.

Previous investigators who recorded the diphasic potential GSR curve agreed in the point that the diphasic potential GSR curve may represent a large response (Darrow 1927; Darrow *et al.* 1956; Fujimori 1955, 1956; Gildemeister 1923).

Fujimori (1955, 1956) pointed out the following as extrinsic factors which may have influence in causing such a diphasic wave form: (1) too short time constant of the amplifier; (2) a faint electric current in the input circuit due to difference of the electromotive forces between electrodes and to the grid current of the amplifier, and (3) activity of the skin under the indifferent electrode. Although careful attempts were made to eliminate these three factors in the present experiment, the diphasic GSR curve still appeared. As a result, it was concluded that diphasic GSR curve might be produced by some intrinsic, namely, physiological processes.

It was also noticed that: (1) there are individual differences in the appearance of the diphasic wave form; (2) the diphasic GSR curve was easily caused to appear following strong stimulation or repeated stimulations; (3) the diphasic GSR easily changed to monophasic following local cooling and it reappeared as a result of re-warming, despite the fact that the control, not the cooled area, continued to show diphasic wave form.

Yokota (1957a) investigated effects of exsanguination on the potential GSR curve applying a tourniquet to the base of a finger and verified that potential GSR curve became monophasic within 15 min. and then gradually diminished in amplitude, even in cases where lowering of skin temperature was prevented by warming the finger, while the control finger still showed diphasic wave form.

Furthermore, Yokota (1957b) proved that pressing one side of the chest changed diphasic wave form to monophasic on the ipsilateral side, while on the contralateral side it remained still diphasic. This result may correspond to the inhibition of sweating due to the "pressure reflex" by Takagi and Sakurai (1950).

Recently Nakayama and Takagi (1958) have also studied the effects of local cooling, of local exsanguination and of pressing the lateral chest wall and have obtained the same results as those of the present authors.

In the present study, the wave form of the potential GSR curve was classified into

four types, bearing in mind the above mentioned results, namely, summarizing the results, the GSR intensified from type *a* to type *d*. The rationality of this classification seems to be supported by the present experimental results.

2. Effects of room temperature upon the potential GSR curve.

According to Kuno (1956), there are two kinds of sweating — mental and thermal. At ordinary temperature, the mental sweating appears only at the palm, soles and axillae. At moderately high temperature, it appears on the whole body surface, but at higher temperature, it vanishes on the palms and soles, while on the other body surface including axillae, it increases.

On the other hand, electrical skin resistance (Richter *et al.* 1943) as well as the GSR of the current method (Fujimori *et al.* 1951) were found to show different responses or manners at the mental sweating areas from those at the thermal sweating areas.

In the present study, the potential GSR changed likewise in different manners at the palm and at the dorsum of hand when the room temperature was changed.

The most distinct differences of the potential GSR at these two areas were: at low room temperature (at 15°C), monophasic GSR curve appeared at the palm, while the GSR frequently failed to appear at the dorsum of hand. At ordinary room temperature (at 20 and 25°C), diphasic GSR curve appeared at the palm, while at the dorsum the GSR curve was rather monophasic. At high room temperature (at 30°C), the diphasic GSR curve appeared both at the palm and at the dorsum, however, at higher room temperature (at 35 and 40°C), the GSR at the palm became rather monophasic, while at the dorsum of hand, the distinctly diphasic GSR curve still appeared.

These results in potential GSR at the palm and the dorsum of hand are similar to those in sweating on these same areas obtained by Kuno (1956). Thus it might be said, in the present experiment, likewise, that (1) the diphasic wave form corresponds to a more highly excited state and the deeper the positive deflection, the stronger the excitation, and that (2) the monophasic change in wave form at the palm at higher room temperature is due to a suppressed mental sweating on that area.

3. Effects of local warming on the potential GSR curve.

As to the effects of local warming on the GSR of the current method, Fujimori, Honma and Watabe (1951) reported that the GSR appeared exclusively at the warmed site of the dorsum of hand, while the other part of the dorsum did not show any resistance change at the room temperature of 20°C or less. This results was re-ascertained in the present experiments by the potential method.

Furthermore, it was observed at both the palm and the dorsum of hand that after local warming, the diphasic potential GSR curve showed more frequently on the warmed hand in comparison with the control hand. These results seem also to support the rationality of the classification of the wave form of the potential GSR curve according to the depth of the positive deflection. However, the change of potential GSR curve from diphasic to monophasic at the warmed area was never observed even when local skin temperature was raised up to 40°C as was recognized at the palm at higher room temperature.

From these results, the change in wave form as well as in latency caused by the rise of room temperature might to some extent be explained by peripheral mechanisms, but the monophasic change of wave form from diphasic at the palm at higher room temperature might be attributed to the central effects of the room temperature as is the case of mental sweating by Kuno (1956).

4. The wave form of the potential GSR curve as an indicator of excitation.

From following experimental results, it might be said that local or central suppression causes monophasic change of the potential GSR curve from diphasic, and that the diphasic wave form with deeper positive deflection corresponds to intensified excitation of the GSR:

(1) The monophasic GSR usually changed to diphasic following strong stimulation or

repeated stimulations. The diphasic potential changes usually corresponded to larger resistance changes which were recorded simultaneously from a different part of the same palm.

(2) The diphasic GSR easily changed to monophasic following local cooling or local exsanguination; both are supposed to lower the excitability of the local skin.

(3) Monophasic change from diphasic was also caused on the ipsilateral side by pressing the lateral chest wall on one side which suppresses the sweating on the ipsilateral side.

(4) At low room temperature, monophasic wave form was more frequently recognized and diphasic wave form with deeper positive deflection increased with the rise of room temperature, but at higher room temperature, the wave form of the GSR at the palm became rather monophasic in accordance with the degree of suppression of the process of mental sweating.

(5) At low skin temperature, monophasic wave form was more frequently recognized, but with the rise of skin temperature caused by local warming, diphasic wave form with deeper positive deflection increased.

As to the mechanism of the appearance of the diphasic potential GSR curve, Darrow *et al.* (1956) expressed their assumption: when the sweating response is insufficient to fill up the sweat ducts, the galvanic electrode picks up electrical changes in tissue surrounding the sweat tubules, whereas with filling of the sweat ducts electrode contact of maximum conductivity is with the interior of the sweat gland. This accounts for the initial negative followed by delayed positive deflections.

Further experiments are needed to ascertain this mechanism, but it may be said so far from our experimental results that there might be two independent components in the potential GSR curve: negative and positive deflections, and that the threshold of the former might be lower than that of the latter. To summarize, it seems to be logical to classify the wave form of the GSR into four types; monophasic and diphasic with graded positive deflection, according to the intensity of the GSR activity.

SUMMARY

The galvanic skin reflex at the palm and the dorsum of hand were investigated on 27 human subjects, changing room temperature and local skin temperature mainly in order to study the mechanism underlying the appearance of the diphasic potential GSR curve.

Experimental factors which might cause the wave form distortion of the potential GSR curve were carefully excluded in the performance of the experiments. Simultaneous recording from the palm and the dorsum of hand was applied so as to enable a comparison of the results with each other.

(1) With the rise of skin temperature as a result of increasing room temperature or of local warming, the potential GSR curve at the dorsum of hand as well as at the palm showed shorter latency.

(2) At the low room temperature of 15°C, the GSR failed to appear in high percentage (67.0 per cent) at the dorsum of hand, while monophasic GSR curve was observed most frequently (53.8 per cent) at the palm.

(3) With the rise of room temperature, it became easier to cause the GSR to appear at the dorsum of hand and the percentage of diphasic GSR curves with deeper positive deflection (type *d*) continued to increase until the room temperature reached 40°C (from 0.8 to 95.2 per cent). The situation at the palm was different from this: the diphasic GSR curve with deeper positive deflection (type *d*) increased in percentage until the room temperature of 30°C (from 24.5 to 52.8 per cent), above which it decreased markedly (8.2 per cent at 40°C); then monophasic wave form increased again. These phenomena at the palm might be attributable to the suppressed mental sweating on the palm at higher room temperature which was found by Kuno (1956).

(4) By means of local warming, it was possible to make shorter the latency of the GSR both at the palm and at the dorsum of hand and to elicit more frequently the diphasic potential GSR curve with deeper positive deflection. However, the change of the wave form from diphasic to monophasic at the palm as was observed at higher room temperature, was not caused by local warm-

ing even when the skin temperature of the warmed area was raised up to 40°C. This might suggest that the suppression of the GSR at the palm at higher room temperature is due to some central mechanism.

(5) The rationality was discussed of classifying the wave form of the potential GSR curve into four types according to the depth of its positive deflection in order to express the intensity of reflex activity.

RÉSUMÉ

On a étudié le réflexe cutané galvanique sur la paume et sur le dos de la main chez 27 sujets humains, en faisant varier la température ambiante et la température cutanée locale, surtout dans le but d'étudier le mécanisme sousjacent de l'apparition de la courbe potentielle diphasique RCG.

Les facteurs expérimentaux qui pourraient occasionner une altération de la forme d'ondes de la courbe potentielle RCG étaient soigneusement exclus dans l'accomplissement de l'expérience. L'enregistrement simultané de la paume et du dos de la main était appliqué afin de permettre la comparaison des résultats l'un avec l'autre.

(1) Lorsque la température cutanée s'élève à la suite de l'élévation de la température ambiante ou d'un réchauffement local, la courbe potentielle RCG sur le dos de la main comme sur la paume montrait une période latente plus courte.

(2) A une température ambiante basse de 15°C la RCG n'apparaissait pas sur le dos de la main dans un pourcentage élevé de cas (67.0 pour cent), tandis qu'une courbe monophasique RCG était rencontrée le plus fréquemment (53.8 pour cent) à la paume.

(3) Avec l'élévation de la température ambiante il était plus facile de faire apparaître la RCG sur le dos de la main et le pourcentage de courbes diphasiques à déflexion positive plus profonde (type *d*) augmentait en pourcentage jusqu'à ce qu'une température ambiante de 40°C fût atteinte (de 0.8 à 95.2 pour cent). Sur la paume de la main la situation en était différente: la courbe diphasique RCG à déflexion positive plus profonde (type *d*) augmentait de pourcentage jusqu'à ce que la température ambiante fût 30°C (de 24.5 à 52.8 pour cent), au-dessus de laquelle elle décroissait de façon marquée (8.2 pour cent à 40°C); puis la forme d'onde monophasique augmentait de nouveau. Ces phénomènes sur la paume pourraient être attribués à la suppression de transpiration sur la paume à une température ambiante élevée telle que découvert par Kuno (1956).

(4) Au moyen de réchauffement local il était possible de faire raccourcir la latence du RCG et sur la paume et sur le dos de la main, et de faire sortir de façon plus fréquente la courbe diphasique RCG à déflexion positive plus profonde. Cependant le changement de la forme d'ondes, sur la paume, du type diphasique au type monophasique, telle qu'observée à une température ambiante plus élevée, n'était pas dû au réchauffement local, même quand la température cutanée de la zone réchauffée atteignait 40°C. Ceci semble suggérer que la suppression de la RCG sur la paume, à une température ambiante plus élevée, doit être secondaire à un mécanisme central quelconque.

(5) On discute la rationnalité de faire classifier la forme d'onde de la courbe potentielle RCG en quatre types selon la profondeur de sa déflection positive, afin de faire exprimer l'intensité de cette activité réflexée.

ZUSAMMENFASSUNG

Der galvanische Hautreflex in der Handfläche und auf dem Handrücken wurde bei 27 Individuen untersucht, wobei die Zimmertemperatur und die Hauttemperatur geändert wurden im Bestreben, den Mechanismus, welcher zum Auftreten einer zweiphasigen Potentialschwankung des galvanischen Hautreflexes zugrunde liegt, aufzuklären.

Experimentelle Faktoren, welche eine Verzerrung dieser Kurve herbeiführen könnten, wurden mit Sorgfalt ausgeschlossen. Gleichzeitige Registrierung von der Handfläche und vom Handrücken wurde ausgeführt, so dass die Resultate gegenseitig verglichen werden konnten.

Die folgenden Befunde wurden erhoben:

1. Mit erhöhter Hauttemperatur zeigte die galvanische Hautreflexkurve auf der Handfläche und auf dem Handrücken eine kürzere Latenzzeit, wobei es nicht darauf

ankam, ob diese erhöhte Hauttemperatur durch erhöhte Zimmertemperatur bedingt war oder infolge einer lokalisierten Erwärmung der Haut auftrat.

2. Bei niederen Zimmertemperaturen von 15°C. trat der galvanische Hautreflex in einen hohem Prozentsatz der Fälle auf dem Handrücken nicht auf (67.0 Prozent), während dem der monophasische Typus der galvanischen Hautreflexkurve am häufigsten auf der Handfläche angetroffen wurde (53.8 Prozent).

3. Bei erhöhter Zimmertemperatur wurde es leichter, den galvanischen Hautreflex zu provozieren, und der Prozentsatz von zweiphasigen Hautreflexkurven mit tieferen positiven Schwankungen (Typus d) nahmen progressiv zu bis die Zimmertemperaturen 40°C erreichten (Anstieg des Prozentsatzes von 0.8 bis 95.2 Prozent). In der Handfläche waren die Verhältnisse verschieden. Die zweiphasische galvanische Hautreflexkurve mit einer tieferen positiven Schwankung (Typus d) nahm im Prozentsatz zu bis zu einer Zimmertemperatur von 30°C. (Anstieg des Prozentsatzes von 24.5 bis 52.8 Prozent), jedoch mit höheren Temperaturen nahm dieser Antworttypus wieder beträchtlich ab (8.2 Prozent bei 40°C.), und die monophasische Antworttypus nahm wieder zu. Diese Verhältnisse in der Handfläche stehen möglicherweise in Beziehung mit einem Verschwinden der psychisch induzierten Schweissekretion in der Handfläche, wie dies bei höheren Zimmertemperaturen gemäss den Beobachtungen von Kuno auftritt.

4. Mit lokaler Erwärmung der Haut war es möglich, die Latenzzeit des galvanischen Hautreflexes sowohl in der Handfläche als auf dem Handrücken zu verkürzen und die zweiphasische Reflexkurve mit tieferer positiver Schwankung häufiger hervorzubringen. Der Wechsel der Kurvenform des galvanischen Hautreflexes der Handfläche von einer zweiphasischen zu einer monophasischen Form, wie sie mit erhöhter Raumtemperatur festgestellt wurde, konnte jedoch mit lokaler Erwärmung der Haut nicht erzeugt werden, selbst wenn die Hauttemperatur bis auf 40°C erhöht wurde. Dies macht es wahrscheinlich, dass das Verschwinden der galvanischen Hautreaktion in der Handfläche bei höheren Zimmertemperaturen durch zentrale Mechanismen bedingt ist.

5. Es wurde besprochen, inwiefern eine Berechtigung besteht, die Kurvenform des galvanischen Hautreflexes in vier Gruppen gemäss der Tiefe der positiven Schwankung zu klassifizieren mit dem Zweck, damit ein objektives Mass zu gewinnen, um die Intensität der Reflexaktivität zu messen.

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THE SUPERSENSITIVITY OF CHRONICALLY "ISOLATED" CEREBRAL CORTEX AS A MECHANISM IN FOCAL EPILEPSY [1]

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Cannon (1939) in his Hughling Jackson lecture enunciated his Law of Denervation and inferred that if it could be extended to the cerebral cortex it might offer a plausible explanation of the mechanism underlying focal cortical epilepsy. He stated: "Is it not possible that tumors, and such lesions of the motor area of the cortex as are associated with the name of Hughling Jackson may induce instability of the neighboring cortical cells by destroying their connections with other cortical cells ? If this should prove to be true, it would be another illustration of the law of sensitization of denervated structures which I have endeavored to illustrate. Here is work to be done — work in which the great neurologist whom we memorialize today would be deeply interested."

In the present research an attempt has been made to test Cannon's hypothesis by investigating two integrally related problems:

1. Is there spontaneous or resting electrical activity in chronically "isolated" [2] cerebral cortex and does this activity resemble that from epileptogenic cortex ?

2. Is "isolated" (denervated) cortex in the chronic state supersensitive to acetylcholine and certain other stimuli and does it behave like epileptogenic cortex on stimulation ?

For many years a controversy has continued as to whether rhythmic electrical activity may exist in cerebral cortex as an inherent property, or whether such cortical rhythms depend upon the interaction of the cortex and subcortical structures.

In support of the spontaneous nature of the cortical rhythms it was shown that bursts of electrical activity are present in cerebral cortex following mesencephalic section of the brain stem of animals (Bremer 1935, 1936, 1938) and after cutting the thalamocortical radiations afferent to a cortical area (Spiegel 1937; Bremer 1938; Swank 1949; Jasper 1949, and others).

The dependence of cortical potentials on subcortical and brain stem mechanisms has been emphasized in the work of Dusser de Barenne and McCulloch (1941), Morison and Dempsey (1942-1943), Dempsey and Morison (1942-1943), Kennard (1943), Obrador (1943), Jasper and Droogleever-Fortuyn (1947), Jasper (1949), Bishop (1949), Moruzzi and Magoun (1949), Lindsley, Bowden and Magoun (1949).

That spontaneous changes in electrical potential may occur from isolated masses of nerve cells was demonstrated in acute experiments on the isolated brain stem of the goldfish (Adrian and Buytendijk 1931), the abdominal and thoracic ganglia of the water beetle (Adrian 1931) and the olfactory bulbs of the frog (Libet and Gerard 1934).

In 1949 Kristiansen and Courtois completely sectioned the neuronal connections to a small area of cerebral cortex in cats and from

[1] This research was supported by a Public Health Service grant from the National Institute of Neurological Diseases and Blindness, and the Robert Clark Memorial Fund.

[2] When the word "isolated" is used in quotation marks it refers to both completely and partially neuronally isolated cerebral cortex.

it in the acute state, recorded bursts of very low voltage rhythmic electrical activity "resembling the normal alpha rhythm". In these neuronally isolated areas of cortex the pial circulation was left essentially intact.

Burns reported that he was unable to record any spontaneous electrical changes from acutely neuronally isolated cortex in cats either under chloralose anesthesia (1949, 1950) or in unanesthetized decerebrate preparations (1951). In these experiments Burns' prime interest was in other aspects of the electrical properties of the cerebral cortex and it was fortunate for his purpose that in most of his preparations spontaneous electrical activity was absent. He observed occasional abnormal bursts of electrical waves in acutely isolated cortex, but believed this activity to be due to injury. Burns (1950) showed that bursting could occur from cerebral cortex connected to the remaining brain by only a few fibres, since nerve impulses presumably entered and triggered the partially isolated cells. Similar bursts he found could be elicited by direct electrical stimulation and he has analyzed these in detail (1950, 1958). Ingvar (1953, 1955) showed that bursting from acutely isolated cortex could be influenced by electrical stimulation of the reticular system in the brain stem.

Periodic bursting was found to occur from the partially isolated human cortex in the acute and chronic state after Scoville undercutting, or lobotomy, by Henry (1949, 1950), and by Henry and Scoville (1952). These rather wide undercuttings in humans were performed by Scoville through a trephine opening in the skull and it seems highly unlikely that the isolations could have been entirely complete, especially in the subpial molecular layer, or at least there is no proof that every nerve fibre to the areas was sectioned.

The presence of spontaneous electrical activity in chronic completely neuronally isolated human and animal cortex was reported by Echlin, Arnett and Zoll (1950, 1952), Echlin and McDonald (1954), and by Grafstein and Sastry (1957) in Burns Laboratory.

The second problem studied in the present investigation was whether cortical neurones become supersensitive to various stimuli following isolation or denervation. Here Cannon's observations are pertinent. In 1939 Cannon, following earlier observations on the supersensitivity of denervated structures by Claude Bernard (1880), Langley (1901), Elliot (1905), and others, published his Law of Denervation.

There is evidence that partial denervation of spinal neurones, whether by posterior root section or hemisection of the cord, sensitizes them to certain stimuli, Mott (1892), Bremer (1928, 1932), Moldaver (1935), Cannon and Haemovici (1939), Cannon, Rosenblueth and Garcia Ramos (1945), Stavraky (1946), Drake and Stavraky (1948), and Teasall and Stavraky (1953).

Stavraky (1943, 1946) and Fisher and Stavraky (1949) have shown that destruction or ablation of one portion of the cerebrum apparently renders descending chains of neurones from that hemisphere supersensitive to the injection of acetylcholine or mecholyl. That cortical neurones may shown an increased sensitivity to electrical stimulation following partial denervation has been reported by Dusser de Barenne and Marshall (1931), Bard (1933), and Obrador (1949). Prolongation of the epileptiform electrical after-discharge following electrical stimulation of the chronically "isolated" cerebral cortex was described by Echlin *et al.* (1953), Echlin and McDonald (1954) and by Grafstein and Sastry (1957). That the resting electrical activity from chronically partially isolated cerebral cortex is similar to that usually regarded as characteristic of epileptogenic cortex was reported by Echlin *et al.* 1952, Echlin *et al.* 1953, and Echlin and McDonald (1954).

There are a number of reports in the literature on the effect of the topical application of acetylcholine on the normal cerebral cortex. Brenner and Merritt (1942) and Forster (1945) found that the topical use of 5 to 10 per cent ACH was usually required to cause epileptiform electrical activity from the cerebral cortex of animals under general an-

esthesia, and Chusid and Mahoney (1953) described similar findings with 10 to 20 per cent ACH on the human cortex. Miller, Stavraky and Woonton (1940) and Chatfield and Dempsey (1942) were unable to precipitate epileptiform electrical discharges from normal cortex (under general anesthesia) with 1 per cent ACH but did obtain such electrical patterns following the use of 1 per cent ACH preceded by 1 per cent eserine. Christiansen and Courtois (1949) similarly produced electrical firing from acutely isolated cortex with ACH preceeded by eserine but made no comparative observations on normal cortex. Purpura (1953) reported selective activation of a local spiking focus in two epileptic patients following the application to the cortex of 2 per cent ACH preceded by 2 per cent eserine.

In 1954 Echlin, and Echlin and McDonald reported that areas of chronically isolated and partially isolated (unanesthetized) cerebral cortex became supersensitive to topically applied acetylcholine, to electrical stimulation and to injections of intravenous Metrazol. In man and monkeys, in whom a small area of cerebral cortex had been neuronally "isolated" 3 to 10 months previously, acetylcholine (0.2 to 1 per cent) was applied (by F.A.E.) to wide areas of the cortex and caused prolonged epileptiform electrical discharges selectively from the "isolated" area, which under certain conditions, spread gradually to wider areas and caused clonic seizures. Subsequent findings by Spiegel and Szekely (1955) suggest that the cerebral sensory cortex may become supersensitive following partial deafferentiation by lesions in the ventral posterior thalamic nuclei. Evidence that the supersensitivity of chronically "isolated" cortex is due to the "isolation factor" and not to injury or ischemia was presented by Echlin (1956). *Recent unpublished observations by Echlin and Battista have shown that the intra-carotid injection of ACH 0.2 micrograms in eserinized monkeys will cause selective rhythmic wave and spike electrical firing from an area of chronically "isolated" cerebral cortex.*

In the present investigation a detailed study was made of the electrical activity which may be recorded from chronic neuronally "isolated" cerebral cortex in monkeys and humans, both before and after various types of stimulation. Much of the work to be described has already been published by the writer in brief preliminary reports.

MATERIAL AND METHODS

In 90 monkeys (macacus rhesus) a large osteoplastic craniotomy was performed under sterile technique (in the Laboratory of Electroencephalography at Lenox Hill Hospital, N.Y.). An area of cerebral cortex approximately 2 to 2½ cm. square and 1 cm. inthickness was (*a*) neuronally isolated by extensive subpial section along 4 sides and wide undercutting (20 preparations) (fig. 1A), or (*b*) partially isolated by section along 3 sides and undercutting (70 pre-

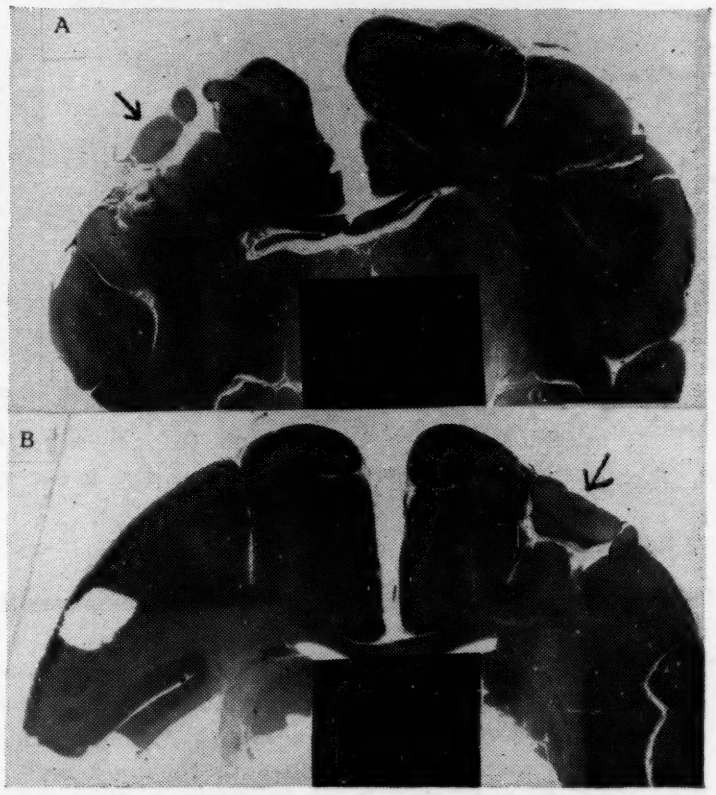

Fig. 1

A. H and E microscopic section of a monkey's brain (no. 50) in which an area of cerebral cortex (indicated by the arrow) was completely neuronally isolated 7 months previously by extensive subpial section of the cortex along 4 sides and undercutting.

B. H and E microscopic section of a monkey's brain (no. 45) in which an area of cerebral cortex (indicated by the arrow) was partially isolated by section along 3 sides and undercutting 8 months previously.

parations) (fig. 1B and 2A, B). The "isolations" were in the frontal lobe in 20 instances and parietal in 70. In each case the pial circulation was left essentially intact. The isolation technique was similar to that described by Kristiansen and Courtois (1949) and Echlin *et al.* (1952) but was performed through tiny stab wounds in the otherwise intact dura mater to avoid the subsequent formation of subdural adhesions. In completely isolating a block of cortex a tiny dural opening was made at each corner of the block, whereas only 2 dural openings, at opposite corners, were required to perform the partial isolations.

In 10 additional monkeys, a unilateral craniotomy was made and the frontal lobe partially isolated by a single subpial lobotomy incision through a small opening.

Two weeks to 3½ years later, under local anesthesia, the cerebral cortex in the 100 monkeys was widely exposed over one (75 animals) or both hemispheres (25 monkeys) after opening the dura mater extensively for the first time. In 80 per cent of the experiments the block of cortex was "isolated" for more than 6 months before reexploration. At this second operation electrocorticograms were made of the resting electrical activity, first through the dura and then directly from the cortex, with a Grass model No. 3D, 6 channel instrument using EEG filters and medium time constants throughout. For recording, bipolar (Penfield-Jasper or Grass) chlorided silver cortical electrodes were used simultaneously from frontal, motor, occipital, temporal and "isolated" cortex. *In all experiments* the tips of the electrodes were approximately 1.5 mm. in diameter and the bipolar leads 4 to 5 mm. apart, except in the human cases when they were approximately 1 cm. apart. The comparative effect on the ECG from "isolated" and from normal cortex was then studied following the wide application to the surface of the brain of acetylcholine chloride, or eserine sulphate (physostigmine sulphate powder) disolved in physiologic solutions of saline at at 37° C., as well as the injection of various drugs as described later. The solutions were topically applied by miostening a long strip of cottonoid (1 cm. in width) with them and laying the strip on the brain from frontal to occipital pole (on one or both hemispheres) crossing the "isolated" zone and touching one of each pair of cortical electrodes. In approximately half the experiments the solutions were buffered with Tris (hydroxy-methyl-amino-methane) to a ph of 7.4 and in the remainder they were not buffered. No definite difference in effect on the cortical activity was noted with the use of buffered or unbuffered solutions provided the per cent of ACH or eserine was kept constant. No change in the ECG was observed following the use of Tris alone. With a few exceptions, described below, the exposed cortex was moistened with physiological saline at 37° C. between applications of the various solutions.

In the treatment of a series of human schizophrenic patients, areas of frontal cerebral cortex were partially or completely neuronally isolated. (On the Neu-

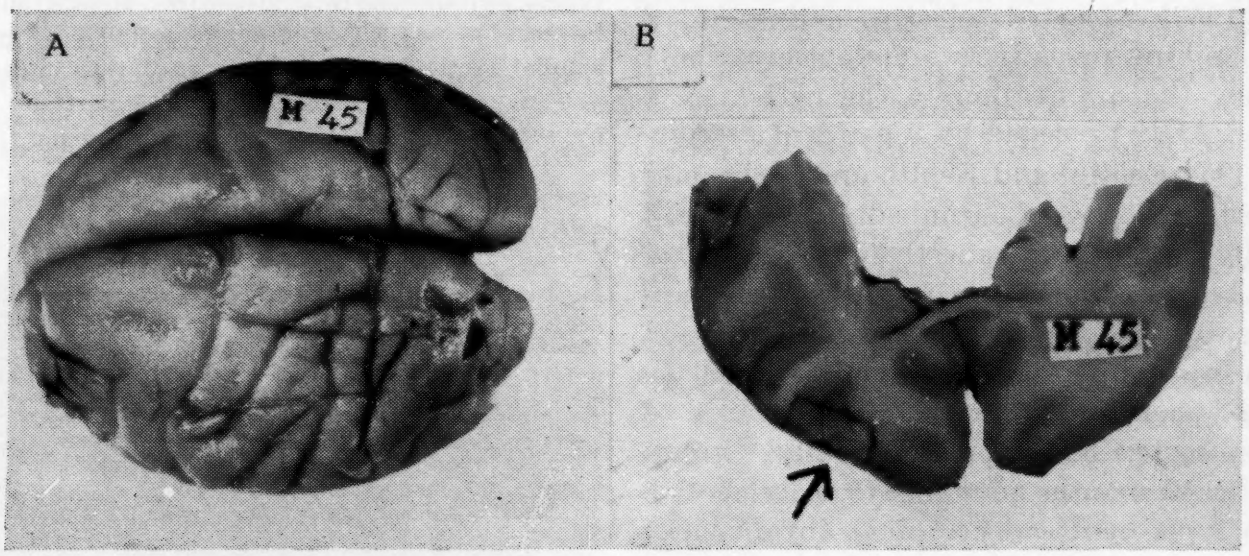

Fig. 2

A. Shows the gross specimen (of no. 45) fixed in formalin with 3 subpial incisions shown.
B. Shows the coronal section of the gross specimen (of no. 45). The arrow indicates the partially isolated block.

rosurgical Service of the NYU-Bellevue Medical Center at Central Islip.) Five weeks to 10 months later electrocorticograms were obtained simultaneously from normal and "isolated" cortex before and after the topical use of acetylcholine.

Studies on the effect of acute temporal lobotomy on the electrocorticograms of 2 patients with temporal lobe epilepsy were made on the Neurosurgical Service of the New York University-Bellevue Medical Center at Bellevue Hospital with Dr. Alec Barnum.

Investigation of electrical bursting from the partially isolated cerebral cortex overlying and surrounding brain tumors has been carried out in 5 cases on the Neurosurgical Service at Lenox Hill Hospital.

RESULTS

Spontaneous electrical activity in chronic neuronally isolated cerebral cortex

"Spontaneous" electrical activity has been recorded from areas of cerebral cortex completely neuronally isolated for 6 months to 3½ years in 20 monkeys and 2 humans (fig. 3). In 5 of the experiments on monkeys the cortex was kept covered with mineral oil from the time of opening the dura until the termination of the recording. In the remaining studies the cortex was irrigated at

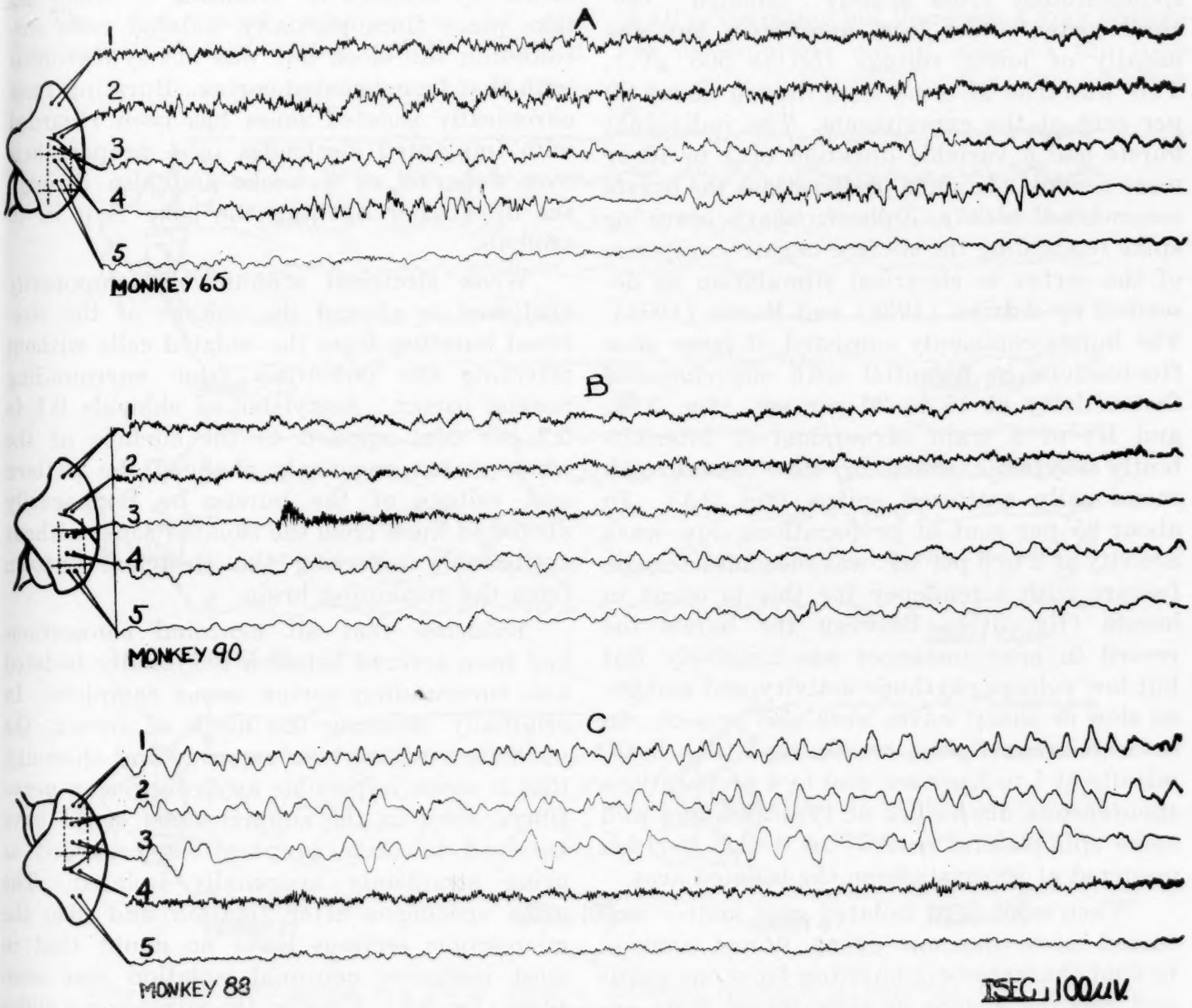

Fig. 3

Three electrocorticograms, A, B and C are shown from 3 monkeys in which an area of cerebral cortex (dotted lines) had been chronically completely isolated (by division along 4 sides and undercutting) for 6 and 9 months (A and C) and for 3½ weeks (B). Note the different types of "*spontaneous*" bursting that may occur from the area of chronically isolated cortex, which in each monkey is outlined by the dotted lines.

frequent intervals with physiological saline solution at 37° Centigrade.

The spontaneous or resting activity was frequently in the form of intermittent bursts (fig. 3) similar to those that follow electrical stimulation (Burns 1951) or occur spontaneously from acutely "isolated" cerebral cortex under local anesthesia, but was usually of lower voltage (50 to 500 μV.). This was true at some time during about 80 per cent of the experiments. The individual bursts had a variable duration of 1 to 10 or more seconds. In some preparations the bursts commenced with a diphasic sharp wave or spike resembling the surface negative response of the cortex to electrical stimulation as described by Adrian (1936) and Burns (1951). The bursts commonly consisted of large slow fluctuations in potential with superimposed fast activity at 15 to 20 per sec. (fig. 3 A, and B) or a train of random or intermittently rhythmic sharp or slow waves with occasionally scattered spikes (fig. 3A). In about 25 per cent of preparations slow wave activity at 2 to 3 per sec. was the characteristic feature with a tendency for this to occur in bursts (fig. 3C). Between the bursts the record in most instances was relatively flat but low voltage rhythmic activity and scattered slow or sharp waves were also present. In several animals slow waves repeated rhythmically at 1 to 2 per sec. and in 4 preparations spontaneous discharges of typical waves and spike epileptiform activity at 2 to 3 per sec. occurred at intervals from the isolated area.

When a block of isolated grey matter contained more than one gyrus, it was common to find characteristic bursting from one gyrus and relative silence or slow waves from another (fig. 3A, B, C). Less commonly bursting was seen synchronously from the whole isolated area. There was a continuous fluctuation and variation in the form, pattern and voltage of the electrical activity with little resemblance to that seen in normal cerebral cortex, suggesting that some humoral factor might be influencing the "isolated" cells.

Evidence that the electrical potentials recorded were actually from the area of isolated cortex was provided in a number of ways. Typical bursting was present over the isolated block, say 2 mm. from a subpial cut along one of its sides, but not from electrodes 2 mm. away over normal brain, or from depth electrodes passed through the block and immediately beneath it. Bursting at times did take place from partially isolated cells surrounding the block but was not synchronous with that from isolated cortex. Bursting from chronically isolated zones has been recorded with implanted electrodes in 4 preparations over a period of 3 weeks and also through the dura after opening the bone flap in 10 animals.

Weak electrical stimulation temporarily abolished or altered the voltage of the electrical bursting from the isolated cells without affecting the potentials from surrounding normal cortex. Acetylcholine chloride 0.1 to 0.2 per cent applied to the surface of the whole cortex commonly changed the pattern and voltage of the bursts, or temporarily abolished them from the isolated zone, without appreciably affecting the electrical pattern from the remaining brain.

Evidence that all neuronal connections had been severed between neuronally isolated and surrounding cortex seems complete. In originally isolating the block of cortex, the methods used were so vigorous and thorough that it seems impossible any connecting nerve fibres, even in the subpial zone, could have survived in these preparations regarded as being completely neuronally isolated. The gross specimens after fixation and also the microscopic sections leave no doubt that in most instances neuronal isolation was complete (fig. 1A). Finally, the microscopic slides revealed the isolated cortex to be in good condition (see below).

The term "spontaneous" has been used to describe the resting electrical changes that may be picked up from the chronically separated area of cortex. Actually the term "spontaneous" should be qualified since it is apparent that certain humoral factors (Purpura 1956) — changes in the pial circulation (Ingvar 1953), stimulation of the reticular

activating system in the brain stem (Ingvar 1953), or even the trauma of operation, may influence the "spontaneous" electrical activity in isolated cortex.

The Gross and Microscopic Appearance of Chronically "Isolated" Cortex

The histological examination of the "isolated" cerebral cortex will be described in a later paper. Preliminary observations of the chronic preparations revealed that an area of cortex could be divided subpially along 3 or 4 sides and undercut without causing evidence of atrophy in the gross specimen (fig. 1 B, 2A and B). However, considerable atrophy of the chronically isolated block was apparent in those experiments where wide undercutting and extensive sectioning of the sides of the block were performed to assure complete destruction of all neuronal connections (fig. 1A). Histologically the six cell layers in the grey matter were well preserved in all preparation but there was a very obvious loss or dropping out of some of the large pyramidal cells. Many nerve cells appeared paler than normal, showed loss of Nissl's substance and an eccentric position of the nucleus. Demyelinization was evident in the subcortical white matter. The cellular changes and loss of myelin were more marked in those preparations where radical sectioning of

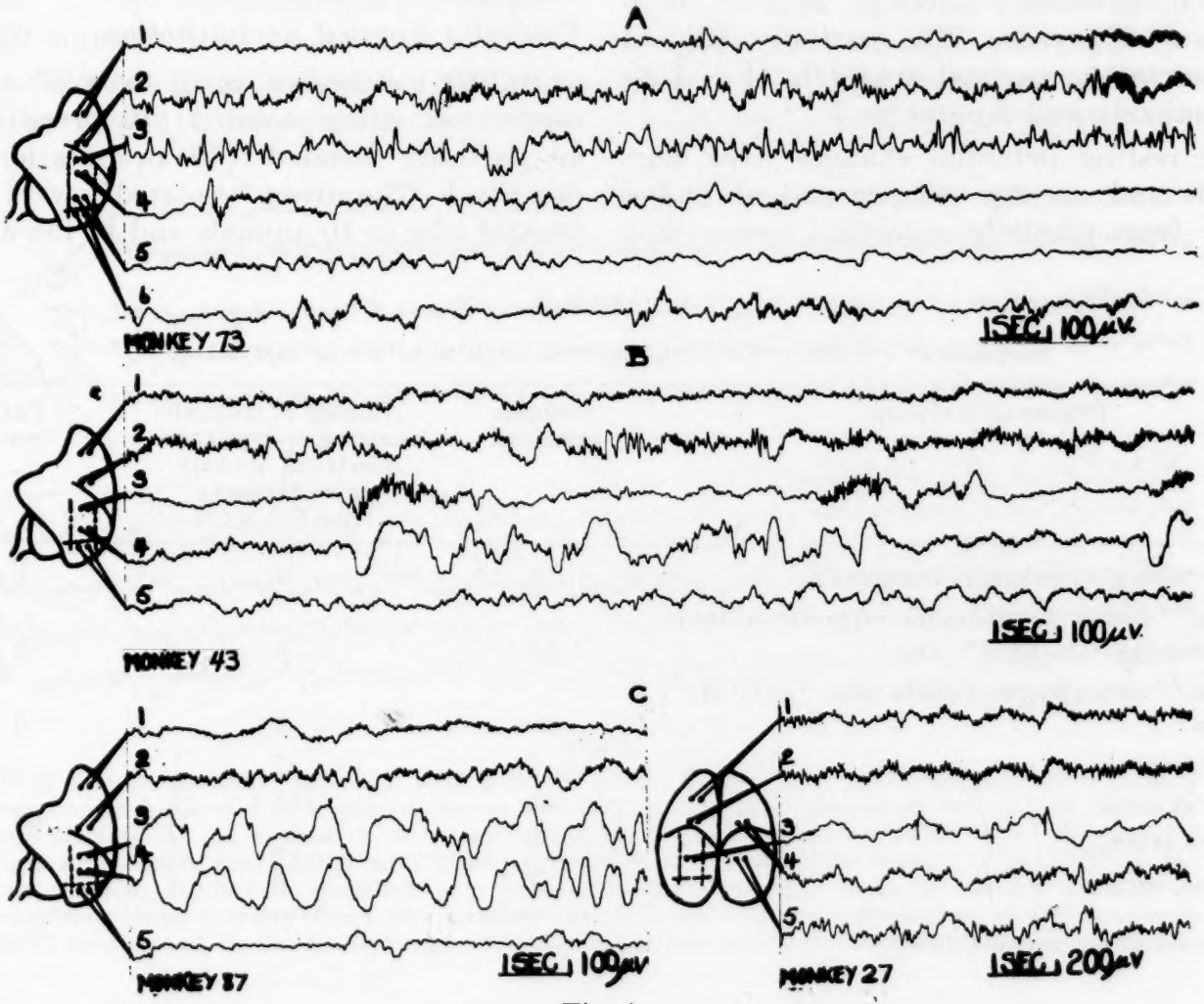

Fig. 4

Four electrocorticograms are shown from 4 different monkeys to illustrate the resting activity from chronically partially neuronally isolated cerebral cortex (subpial division along 3 sides and undercut 6 months to 3¼ years previously). Note that bursting is confined to the partially isolated block of cortex, except in A channel 6, where some bursting is also present over the partially isolated occipital lobe.

neural connections was carried out to assure total neuronal isolation.

"Resting" Electrical Activity from Chronically Partially Isolated Cerebral Cortex

Electrocorticograms were obtained from 60 monkeys (fig. 4 and 6 A) and 3 humans (fig. 10 I) in whom a block of cerebral cortex had been chronically partially isolated for 6 months to 3¼ years. The partially isolated zone was in the parietal area (fig. 4 and 6) in 63 animals and frontal in 7.

The resting potential changes were more unstable and usually sharper and of higher voltage from partially separated cortex than when neuronal isolation was complete. Rapid fluctuations in the pattern and voltage of the electrical waves were commonly greater where partially isolated cortex bordered on normal brain at the open, unsectioned end of the block (fig. 4). From the closed end of the isolated zone, large slow, often rhythmic, fluctuations in potential were common with relatively flat record intervening (fig. 4).

Paroxysmal bursting of the type seen in acutely "isolated" cortex was, at intervals, present in the majority of preparations (fig. 4 and 6 A). In addition, there occurred random sharp activity with scattered slow waves and commonly random spikes (fig. 4 and 6 A). Rhythmic high voltage (500-1000 μV.) spike, or wave and spike activity at about 1 to 3 per sec. was recorded from partially isolated grey matter as a resting phenomena, at intervals, in many animals.

The Supersensitivity of Chronically "Isolated" Cerebral Cortex to Topically Applied Acetylcholine

In 80 monkeys a small area of cerebral cortex was either isolated (10 preparations) or partially isolated (70 preparations), as described. The areas "isolated" were in the frontal lobe in 10 animals and in the anterior parietal region in 70 (fig. 5 and 6). Two weeks to 3½ years later (6 months to 3½ years in 60 animals) the old osteoplastic bone flap was re-elevated, the dura widely opened for the first time and the brain over most of the lateral aspect of the hemisphere exposed. In 70 animals electrocorticograms with bipolar recording, were made simultaneously from frontal, motor, temporal, occipital and isolated cortex (fig. 5 and 6). In the other 10 monkeys simultaneous records were obtained of the electrical activity from multiple areas in the opposite normal hemisphere, as well as from

TABLE I

Response of frontal, parietal or temporal cerebral cortex to acetylcholine

Degree of isolation	Animals examined	Number of animals showing epileptiform electrical activity in response to 0.2-0.5% ACH	Per cent
Normal cortex, previously unoperated	9	0	0
"Normal" cortex in hemisphere opposite to that containing "isolated" area	10	0	0
"Normal" cortex in hemisphere with "isolated" area	80	0	0
Partial frontal	7	7	90
Partial parietal	63	57	
Complete frontal	3	2	
Complete parietal	7	6	

The isolation were all chronic.

the hemisphere containing the ''isolated'' zone. A strip of cottonoid, 1 cm. in width, was soaked in 0.2 to 1 per cent acetylcholine and laid on the brain from frontal pole to occiput crossing the ''isolated'' zone, so that it contacted one of each pair of electrodes. In this manner the comparative effect of topically applied ACH on the ECG from normal cerebral cortex in different areas and from ''isolated'' cortex was studied simultaneously in the 80 animals.

The cottonoid strip soaked in ACH was allowed to remain in contact with the surface of the pia-arachnoid for 1½ to 10 min. In many preparations no pronounced effect was noted until the ACH had been applied for 1½ min. on 2 or more occasions at 3 to 5 min. intervals.

When 0.2 to 0.5 per cent acetylcholine was placed widely on the brain, as described, it caused high voltage rhythmic slow wave and spike discharges selectively from the ''isolated'' frontal or parietal cortex in 90 per cent of the 80 chronic preparations tested (fig. 5 and 6, table I); 0.2 per cent ACH was sufficient to precipitate such epileptiform discharges selectively from the ''isolated'' area in over 60 per cent of the animals (fig. 5) and 1 per cent ACH fired the isolated cortex in those 8 preparations unresponsive to 0.2 or 0.5 per cent ACH (fig. 7).

These findings are in striking contrast with the observation that 0.2 to 0.5 per cent ACH never caused epileptiform discharges when used topically on frontal or anterior parietal cortex in the hemisphere homologous to one containing a chronically isolated block of grey matter (10 preparations) or on normal (unanesthetized) frontal or anterior parietal cortex of previously unoperated monkeys (9 preparations) (see table I).

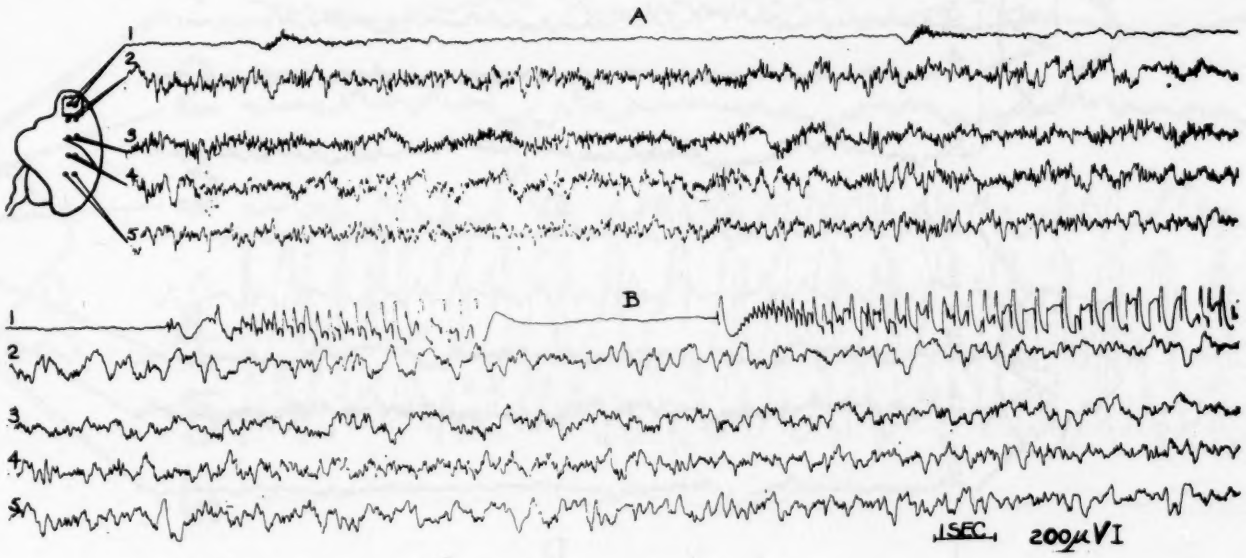

Fig. 5

ECG from a monkey (no. 24) with a small area (dotted lines) of cerebral cortex totally neuronally isolated for 6 mos. A shows the resting electrical discharge before any form of stimulation. In A, channel 1, are seen bursts of ''spontaneous'' activity from the isolated cortex. B shows the EEG 2 min. after application of 0.2 per cent ACH for 1½ min. to the cortex from frontal to occipital pole as described. Note that there is selective firing of rhythmic burst activity from the isolated zone. After several applications of 0.2 per cent ACH this type of rhythmic discharge continued at periodic and later irregular intervals for hours.

In isolating a block of parietal cortex fibres to the occipital pole were of course sectioned thus partially isolating an area of occipital cortex. It was found that this partially isolated occipital cortex was more sensitive to ACH than normal grey matter and this phenomenon, as well as the response of normal unanesthetized cortex to ACH, is being further investigated (by Echlin, F. and Battista, A.).

From these observations it is evident that

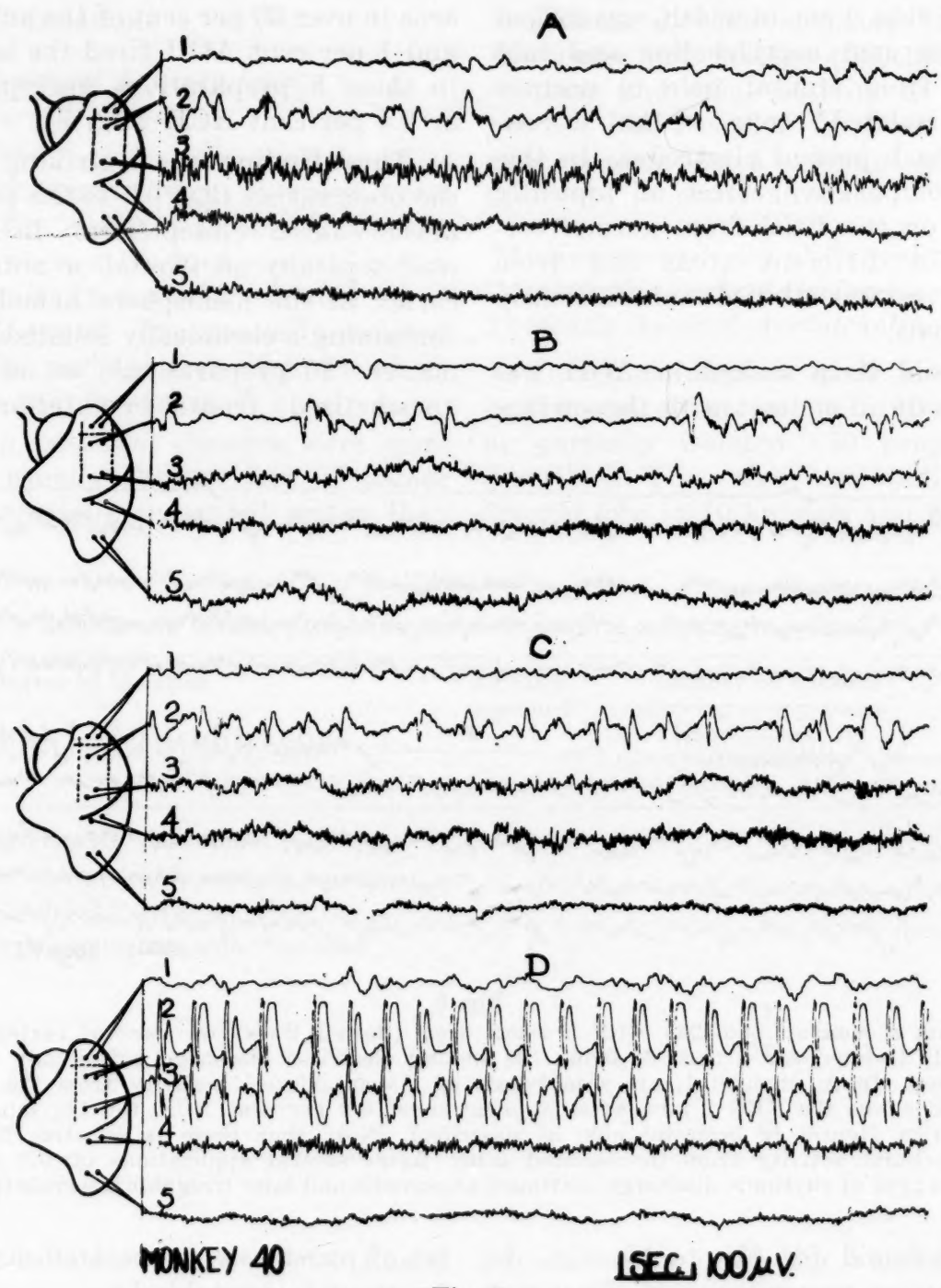

Fig. 6

Characteristic ECG from a monkey in which an area of cerebral cortex was partially neuronally isolated 6 mos previously (outlined by dotted lines).

A channel 2 and 3, shows the resting electrical discharge from the partially isolated zone. In B note the change 2 min. following the application of 0.2 per cent acetylcholine for 1½ min. to the cortex from frontal to occipital pole (as described). Periodic bursting is now more evident. In C 0.35 per cent ACH has been applied widely to the cortex in the usual manner for 3 min. and the record taken 3 min. later. Note the random spiking which tends to become periodic from the most isolated zone. In D is shown the effect of the application of 0.35 per cent ACH to the cortex for 3 min. for a second time. Typical 2 to 3/sec. wave and spike activity has now appeared selectively from the partially isolated area and continued uninterruptedly for 5 min.

chronically ''isolated'' frontal or parietal cerebral cortex is supersensitive to the topical use of 0.2 to 0.5 per cent ACH as compared to normal cortex in these areas.

The most characteristic features of the abnormal electrical discharges precipitated selectively from the ''isolated'' zone by the use of ACH were their rhythmic pattern and the fact that they nearly always became wave and spike in form (fig. 5 and 6). Their frequency varied, often being rapid at the onset with a tendency to slow to 1 to 2 per sec. before ceasing (fig. 5 and 6).

The abnormal rhythmic potentials from ''isolated'' cortex usually appeared about 90 sec. after removal from the brain of the cottonoid strip soaked in ACH. This was true particularly after application of the ACH for 1½ min. but occurred at this time interval in some preparations where the ACH was left in contact for 3 to 10 min. Once wave and spike electrical waves had occurred from the ''isolated'' region they had a tendency to reappear at irregular intervals for long periods and frequently for many hours, especially when 0.5 to 1 per cent ACH was used. If 0.5 per cent ACH was required to initiate the high voltage activity, usually 0.2 per cent ACH was sufficient thereafter to bring on such firing selectively from the ''isolated'' block.

The supersensitivity to acetylcholine, as described, was present to some degree within two weeks following partial neuronal isolation, about maximum in 6 months, and still pronounced after 3½ years. The criteria used in an attempt to estimate roughly the degree of supersensitivity of ''isolated'' cortex to ACH were:

A. The per cent of ACH (0.2 to 1 per cent) and the duration of its application necessary to produce epileptiform discharges.

B. The duration, voltages and general intensity of the discharges.

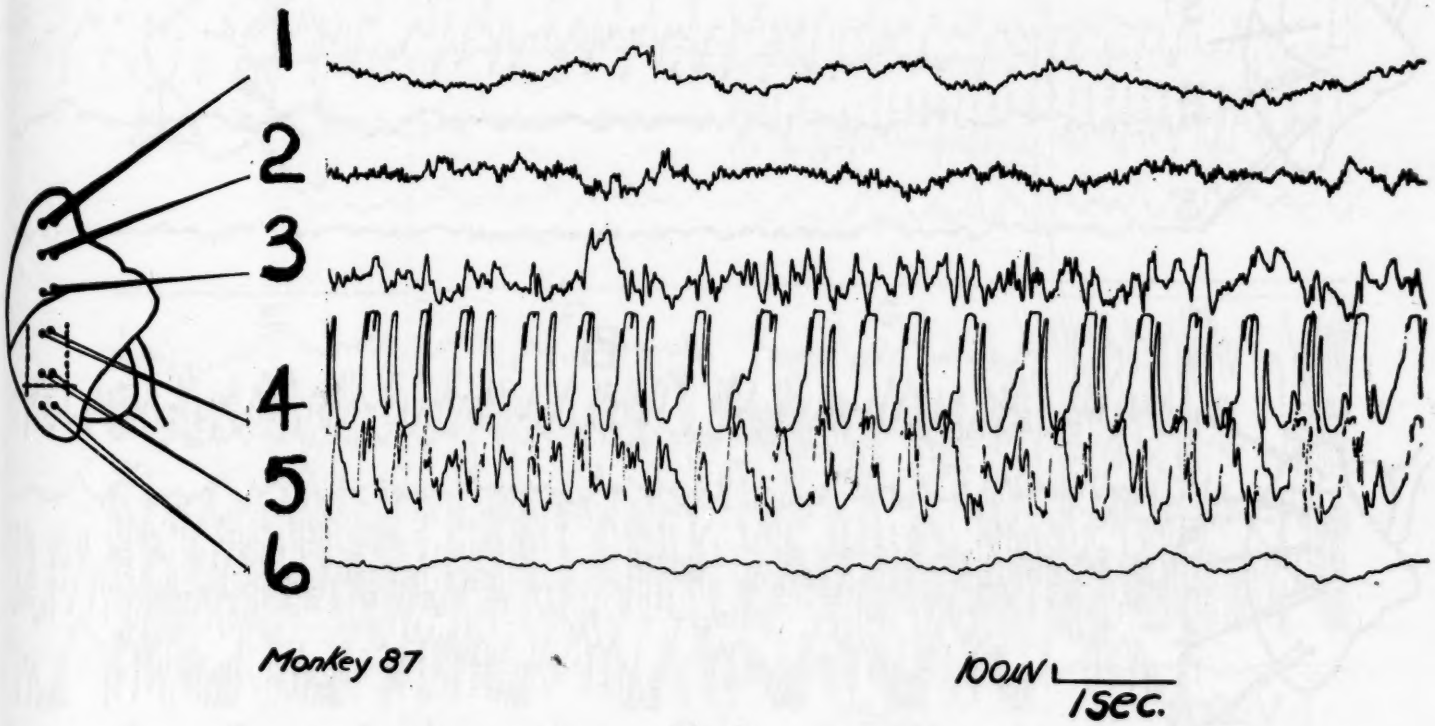

Fig. 7

This is an ECG from a monkey with an area of cerebral cortex (dotted lines) partially isolated (divided along 3 sides and undercut) 18 months previously. One per cent ACH had been topically applied for 2 min. to the brain from frontal pole to occiput 4 min. previously. Note the selective epileptiform electrical firing from the partially isolated cortex in channels 4 and 5. This type of discharge continued for 10 min. No such abnormal firing occured in any preparation when 1 per cent ACH was applied simultaneously to the ''normal'' cortex of the opposite hemisphere.

C. The degree of their spread to neighboring cortex including the precipitation of clinical seizures.

In many animals the "isolated" area contained a portion of 2 or more gyri. High voltage electrical activity precipitated by ACH commonly occurred from only one of these gyri at a time. As the discharge diminished over one gyrus it appeared or increased over another, and thereafter there was alternate firing with less frequently synchronous discharge from the whole "isolated" block. This "will-o-wisp" activity is reminiscent of that described by Walker (1948) and by Meyers (1954) in the human cortex of epileptic patients around an area of scaring where at least some cortical neurones must have been partially isolated.

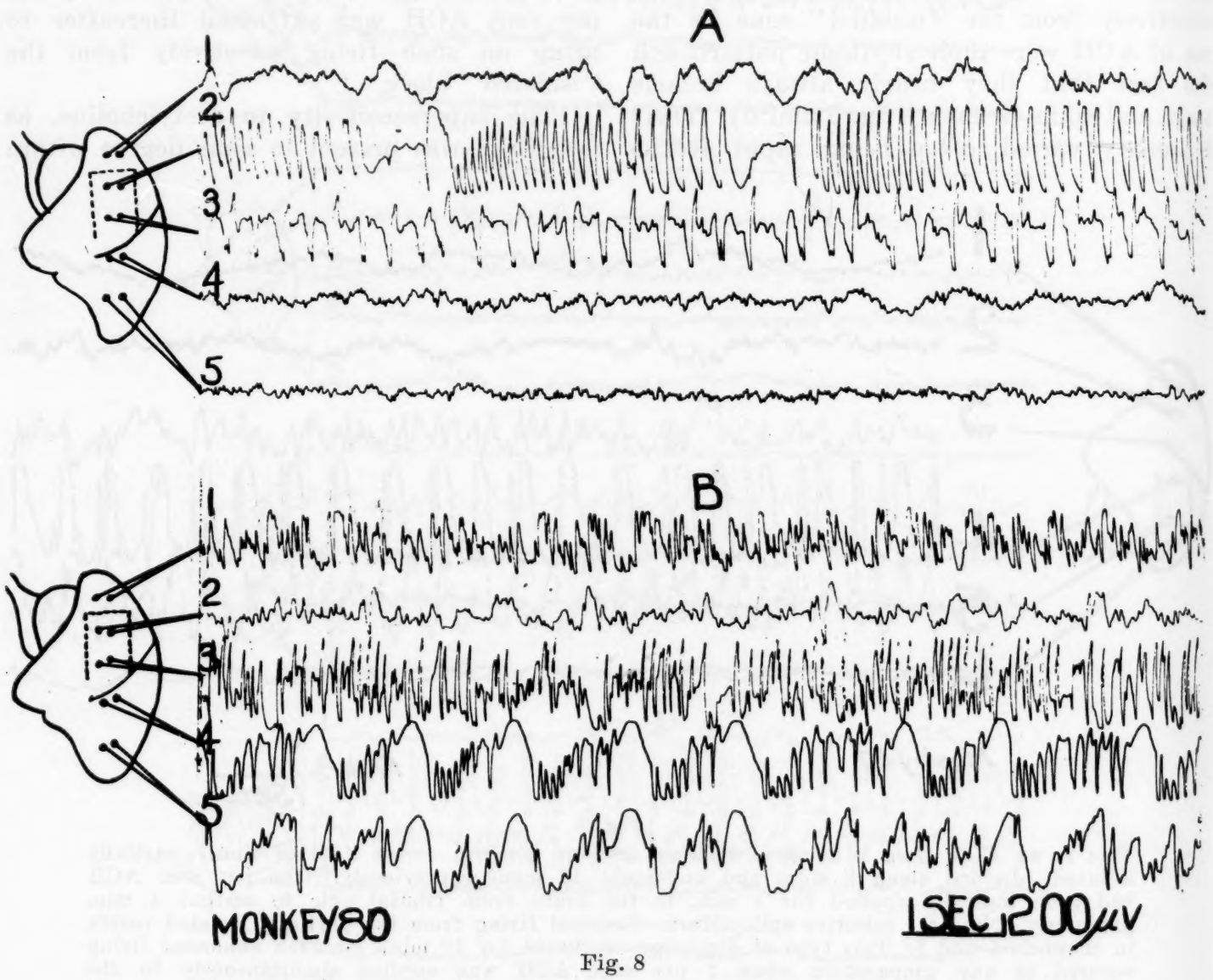

Fig. 8

Electrocorticogram from a monkey with an area of cerebral cortex partially isolated by subpial section along 3 sides and undercutting months previously.

A. ECG 4 min. following the wide application of ACH 0.5 per cent to the cortex from frontal pole to occiput for 2 min. Note that the abnormal electrical firing is confined to the partially isolated block.

B. ECG showing the effect of a similar application of 0.5 per cent ACH preceeded by the application of one per cent eserine. Note that the abnormal discharge has now escaped from the partially isolated cortex and has involved the entire surface of the hemisphere. Clonic movements are occurring from the opposite extremities.

ACH in dilutions of 0.1 to 0.5 per cent usually caused an increase in the voltage of

the individual "spontaneous" bursts from "isolated" cortex (fig. 6B), either before the onset of typical high voltage rhythmic potentials, or after such an outburst had subsided. Occasionally following the application of ACH to the brain, the high voltage sharp wave discharge (fig. 6C). In addition ACH, in some animals, caused the spontaneous random very large slow waves, that occurred over "isolated" cortex, to appear in a rhythmic fashion.

The findings in this large series of experiments have confirmed the earlier observa-

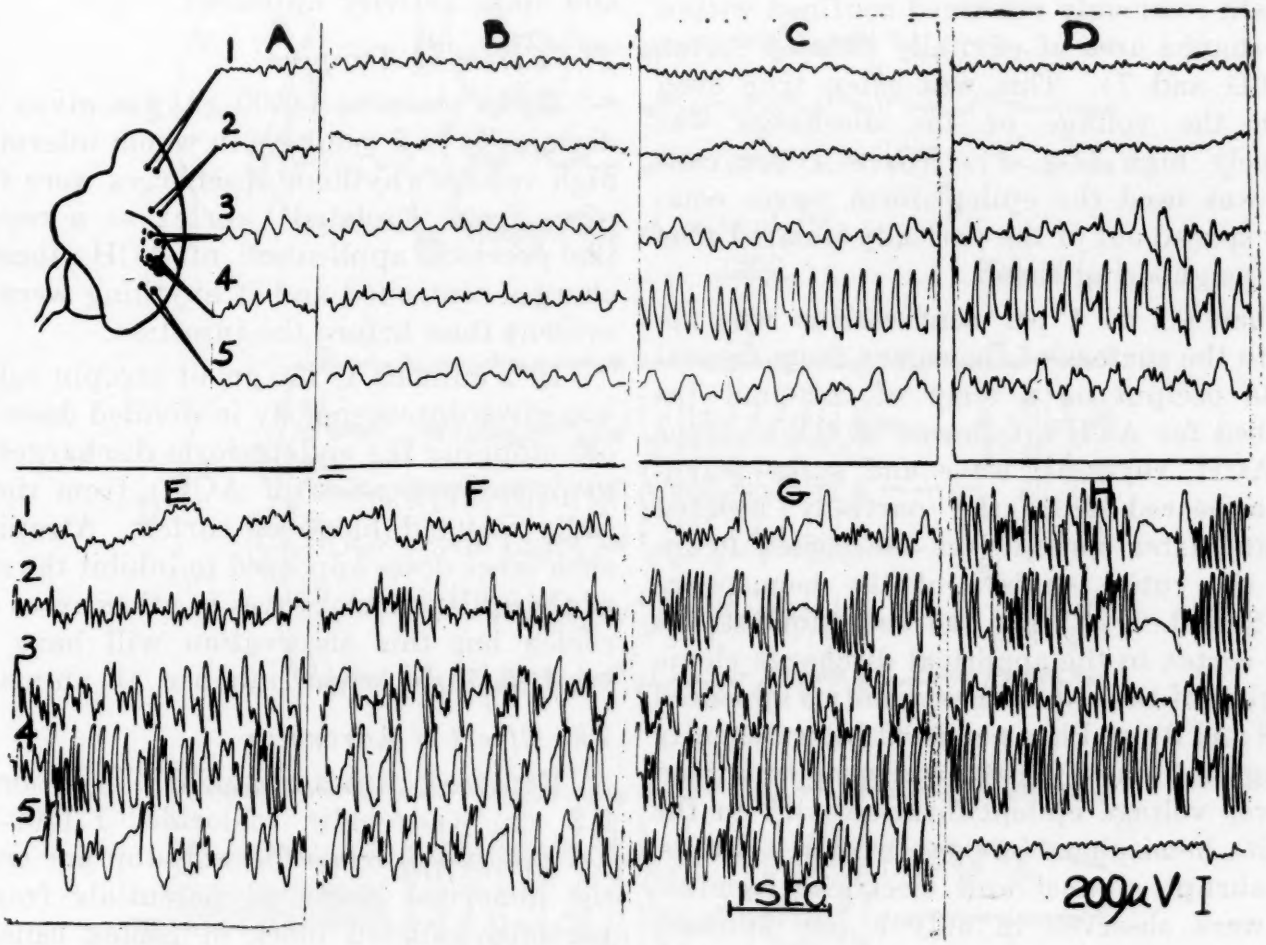

Fig. 9

ECG from a monkey (no. 27) with a portion of brain partially isolated in the post central and parietal area (dotted lines) for 6 months.

A, resting electrical pattern.

B to H, evolution of an epileptiform electrical discharge as a result of the application of eserine 1 per cent followed by ACH 0.1 per cent to the brain from 1 to 5. The discharge starts in channel 4 at B and gradually increases in voltage and spreads forward over the cerebral cortex in the left hemisphere. H is the same as G except that channel 5 is for the first time recording from the right cerebral cortex at a point homologous to 4. Note that the discharge has not spread to the right hemisphere. In G and T the animal was having clonic movements of the right fore and hind limbs. Six min. elapsed between C and H. The generalized discharge continued during the remaining 2 hours of recording and intermittently spread to the opposite hemisphere.

or spike that initiated the onset of a spontaneous burst, was repeated rhythmically at gradually increasing frequency until it appeared to become part of an epileptiform

tions (Echlin 1954; Echlin and McDonald 1954) that neuronally "isolated" monkey cerebral cortex, in the chronic state, is supersensitive to topically applied acetylcholine.

The Spread of Epileptiform Electrical Activity from Partially Isolated Cortex following the Application of ACH and of Eserine and ACH

Abnormal electrical discharges precipitated in the manner described by the application of 0.2 to 1 per cent ACH to wide areas of the brain commonly remained confined within the U-shaped area of partially isolated cortex (fig. 6D and 7). This was often true even though the voltage of the discharge was extremely high (fig. 7). When 1 per cent ACH was used the epileptiform waves commonly spread out of the partially isolated zone to the neighboring cortex.

When 0.2 to 1 per cent eserine was applied to the surface of the cortex from frontal pole to occiput on a strip of cottonoil (as described for ACH), followed by 0.2 to 1 per cent ACH, rhythmic wave and spike potentials appeared from the partially isolated zone and later spread over the cortex to involve the entire surface of the hemisphere (fig. 8 and 9). With the inclusion of the motor cortex in the abnormal discharge clonic twitching of the opposite extremities appeared (fig. 8 and 9) and has persisted intermittently as long as 5 days. There was usually spread of lower voltage epileptiform activity to the opposite hemisphere but generalized seizures, with abrupt clinical and electrical termination, were observed in only a few animals. After a period of minutes or longer, the abnormal waves usually receded again into the partially isolated zone where they often continued intermittently for hours. It was not uncommon to see the abnormal discharge under discussion repeatedly spread forward to the motor area and as often recede again in the manner described.

Following the intra-muscular injection of eserine, epileptiform electrical potentials were precipitated from "isolated" brain with weaker solutions of topically applied ACH than had been required previously. If rhythmic wave and spike discharges had been present in the "isolated" area as the result of the prior application of ACH, intramuscular eserine frequently resulted in a reappearance of these discharges even though they had been absent for more than half an hour before its injection. In only 2 preparations was 0.5 per cent eserine applied widely to the cortex before acetylcholine. In these animals there was an increase in the voltage of the bursts from the "isolated" cortex but no rhythmic wave and spike activity appeared.

The Effect of Atropine

When atropine 1/600 gr. was given hypodermically to 5 monkeys in whom intermittent high voltage rhythmic discharges were taking place from "isolated" cortex as a result of the previous application of ACH, these discharges continued and if anything were more evident than before the injection.

In 2 animals 1/150 gr. of atropin sulphate was given intravenously in divided doses without stopping the epileptiform discharges (due to prior application of ACH) from the partially isolated block of cortex. Atropine in such large doses appeared to inhibit the spread of the epileptiform waves to other areas of the cortex but this observation will have to be verified in a larger number of animals.

The Effect of Adrenalin

Repeated intra-muscular injections of 0.2 cc. (adrenalin chloride 1:1000-Parke Davis) in 4 animals did not stop nor enhance the abnormal electrical potentials from the partially isolated block of cortex caused by ACH and eserine, but it may have had an inhibitory effect (see Marrazzi 1943) on the spread of such discharges.

The Question of Spread of Epileptiform Activity into or from Completely Neuronally Isolated Cortex

In 3 animals in whom an area of parietal cortex had been completely neuronally isolateded 2 to 3½ years previously, spontaneous high voltage rhythmic wave and spike activity arising in the occipital lobe appeared subsequently to spread to the isolated cortex. In 2 monkeys with cortex similarly isolated for more than 6 months, generalized epileptiform activity occurred throughout a cerebral hemisphere after the intra-muscular injection

of eserine and the topical application of ACH to wide areas of the cortex. These prolonged generalized discharges at intervals stopped abruptly throughout the hemisphere and only a few seconds later ceased in the neuronally isolated block, suggesting that the activity within the isolated area was not entirely independent of that occurring in the remainder of the brain.

Electrical stimulation of normal brain in

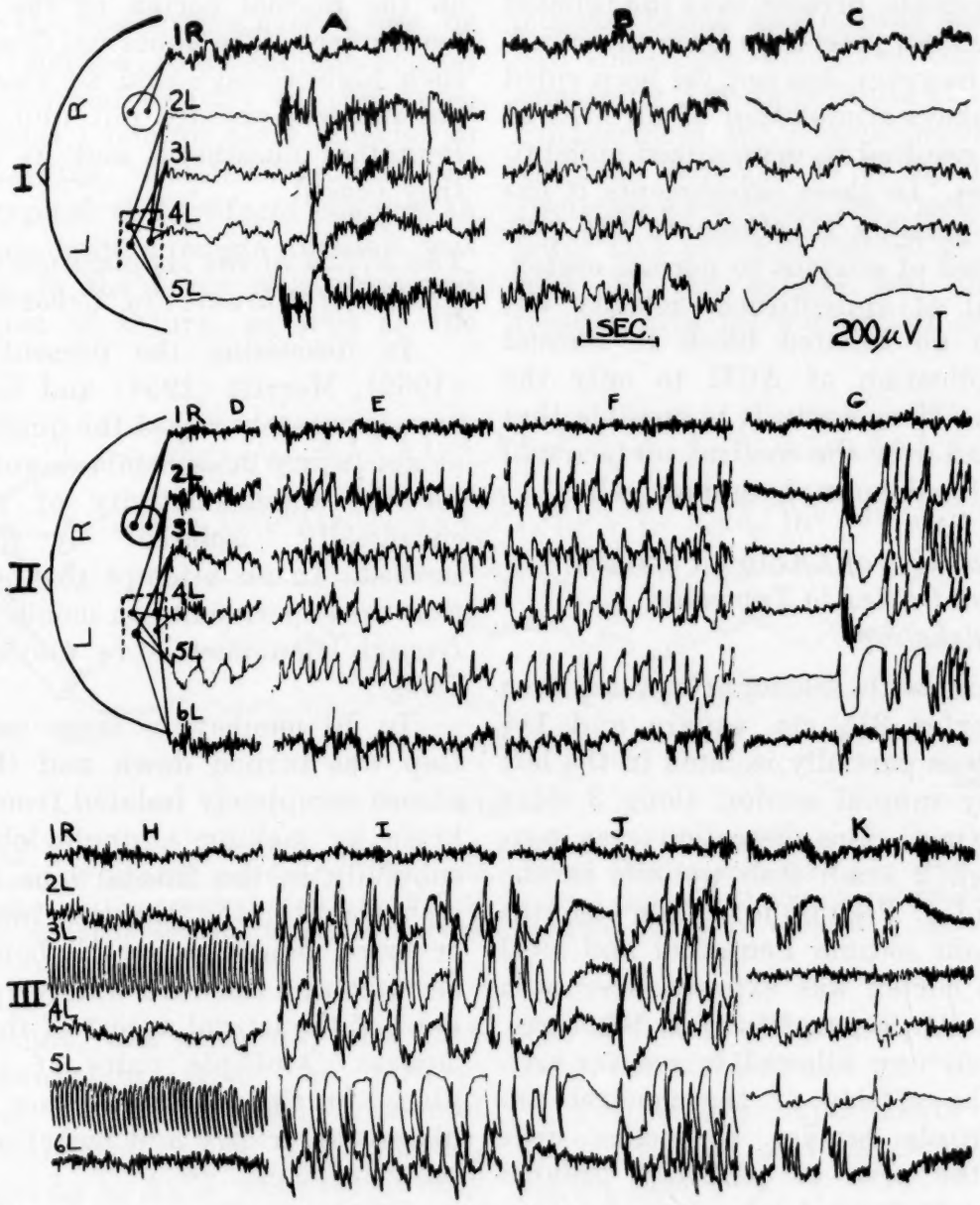

Fig. 10

This is an ECG under light sodium Pentothal anesthesia from a patient (A.R.) with schizophrenia, in whom an area of cortex in the left frontal lobe was partially isolated (dotted lines) 10 months previously (see text).

(I. Shows the resting ECG. In ABC is seen a characteristic burst (lasting 20 sec.) of electrical activity from the partially isolated zone.

II and III shows the ECG following the irrigation of 5 cc. of 0.2 per cent ACH for 1½ min. simultaneously onto the partially isolated cerebral cortex in the left frontal lobe (channel 2 to 6) and onto the normal cortex in the right frontal lobe (channel 1). Note that the ACH has caused a rhythmic epileptiform electrical outburst from the partially isolated zone (channels 2 to 6) but has had no appreciable effect on the electrical pattern from the normal cerebral cortex in channel 1. E. was taken 2 minutes following the application of 0.2 per cent ACH. The duration of the discharge E to K was 2½ min. with cessation at K, following the rapid use of sodium Pentothal intravenously.

5 animals resulted in generalized epileptiform electrical activity which appeared to spread to chronic neuronally isolated cortex, as described in acute preparations by Livingston *et al.* (1956). The possibility that the epileptiform potentials, present over the isolated area, may have been picked up from surrounding cerebrum, however, has not yet been ruled out. In 3 monkeys stimulation of an area of isolated brain resulted in generalized epileptiform discharges. In these experiments it has not yet been possible to eliminate the possibility of spread of current to normal cortex. Similar spread of epileptiform activity has occurred from an isolated block to normal cortex on application of ACH to only the isolated region. Here again it is possible that the ACH spread over the cortical surface and directly stimulated normal cerebral cells.

The Supersensitivity of Chronic Partially Isolated Human Cortex to Topically Applied Acetylcholine

In a patient with schizophrenia an area of cerebral cortex 3½ cm. square and 1½ cm. in depth, was partially isolated in the left frontal lobe by subpial section along 3 sides and undercutting. The dissection was performed through 2 small stab wounds in the dura (see under Technique). Ten months later under light sodium Pentothal and local anesthesia the cortex was exposed over both frontal lobes in preparation for lobotomy. The patient was now allowed to recover partially from the effects of the general anesthesia. Multiple bipolar electrodes were placed over the area of partially isolated cortex in the left frontal lobe and also over the normal right frontal cortex and ECGs taken. As shown in figure 10A, B, C frequent prolonged spontaneous bursts of abnormal activity lasting 20 to 30 sec. and preceded by a high voltage spike (300-800 μV.) were recorded from the area of partially ''isolated'' brain in its resting state.

Five cc. of 0.2 per cent ACH chloride were now irrigated onto the partially isolated cortex in the left frontal lobe and simultaneously an equal quantity of ACH was irrigated on the normal cortex in the right frontal area. One and ½ min. later high voltage rhythmic epileptiform spike discharges occurred from the ''isolated'' area in the left frontal lobe (fig. 10D to K) but the ACH had no apparent effect on the normal cortex in the right cerebral hemisphere. The abnormal discharges were of such high voltage and so alarming that the patient was rapidly put under deep sodium Pentothal anesthesia and in a few minutes they ceased.

The Effect of the Application of ACH on the Cortex of Chronically Lobotomized Monkeys

In discussing the present work, Jasper (1952), Merritt (1954) and Kennard (1954) have separately raised the question of whether or not injury or ischemia might be responsible for the supersensitivity of cerebral cortex chronically ''isolated'' by the method described. In an attempt to answer this question the experiments on monkeys with chronic frontal lobotomies were undertaken (Echlin 1956).

In 10 monkeys a large osteoplastic bone flap was turned down and the frontal lobe almost completely isolated from the remaining brain by making a single lobotomy incision subpially in the frontal lobe through a tiny stab wound in the otherwise intact dura. Seven or more months later the bone flap was reelevated and the dura widely opened, exposing most of the lateral aspect of the cerebral hemisphere. Multiple pairs of electrodes were placed on the cortical surface at points equidistant anteriorly and posteriorly to the lobotomy incision.

ECGs of the resting activity from the ''isolated'' frontal lobe revealed random slow waves or bursts of random or rhythmic slow waves but no paroxysmal bursting of the type seen over small areas of undercut and ''isolated'' cortex.

When 0.2 to 0.5 per cent ACH was placed widely on the brain in the usual fashion there was some build-up in voltage of the activity over the ''isolated'' frontal lobe and large, often rhythmic, slow waves commonly appeared. After the wide application to the

cortex of 0.75 to 1 per cent (or occasionally 1.5 per cent) ACH for 1½ or more minutes, prolonged intermittent high voltage rhythmic bursts of wave and spike activity appeared over the frontal cortex, anterior to the lobotomy incision (fig. 11). Electrodes placed elsewhere over the hemisphere even 1 mm. or more posterior (caudad) to the subpial incision revealed no abnormal activity of this type, whereas electrodes 1 mm. or more anterior to the incision over the ''isolated'' frontal lobe recorded the typical epileptiform changes in potential. Since only a single incision was made subpially in the brain it is presumed that the amount of injury, as well as the degree of ischemia, was essentially the same at points equidistant from the incision anteriorly over the lobotomized area and posteriorly over normal cortex. Yet, as noted, the supersensitivity to ACH was present only over the ''isolated'' frontal cortex.

These findings seem to prove that, what we have termed, ''the isolation factor'', as opposed to injury or ischemia, is the important one in the causation of the supersensitivity of neuronally ''isolated'' cerebral cortex (Echlin 1956).

Following the intra muscular injection of eserine (0.1 mg. to 0.5 mg.) there was some increase in voltage and slowing in frequency of the ''isolated'' frontal lobe resting potentials. If ACH had previously been applied to the cortex, intra-muscular eserine at times brought on recurrent outbursts of high voltage rhythmic wave and spike activity restricted to the ''isolated'' frontal cortex even though such discharges were absent for 15 minutes before eserine was used. Such localized discharges sometimes continued for the remaining 2 or more hours of the experiment. Furthermore the concentration of the ACH solutions required to bring on epileptiform electrical waves from the ''isolated'' area were lower (0.2 per cent instead of 0.75 to 1.5 per cent) if the animal had previously been treated with intra-muscular eserine.

Fig. 11

This is an ECG from a monkey (no. 5) in which a left frontal lobotomy was performed, as described, 6 months previously. This min. before this tracing 0.75 per cent ACH had been applied to the cerebral cortex from 1 to 5, for 3 min. Note the characteristic selective firing of rhythmic activity from the partially isolated cortex in channel 1 and 2 anterior to the lobotomy incision.

The Effect of Electrical Stimulation and of Intra-venous Metrazol on ''Isolated'' Cortex

Preliminary experiments (Echlin *et al.* 1953; Echlin and McDonald 1954) have shown that:

A. Following electrical stimulation the electrical after discharge is much more prolonged from chronically ''isolated'' monkey cerebral cortex than from normal or acutely ''isolated'' cortex.

B. Intravenous injections of Metrazol caused selective electrical firing from chronically ''isolated'' cortex.

These experiments are being continued.

In preliminary studies by Echlin and Battista it has been found that intra-carotid in-

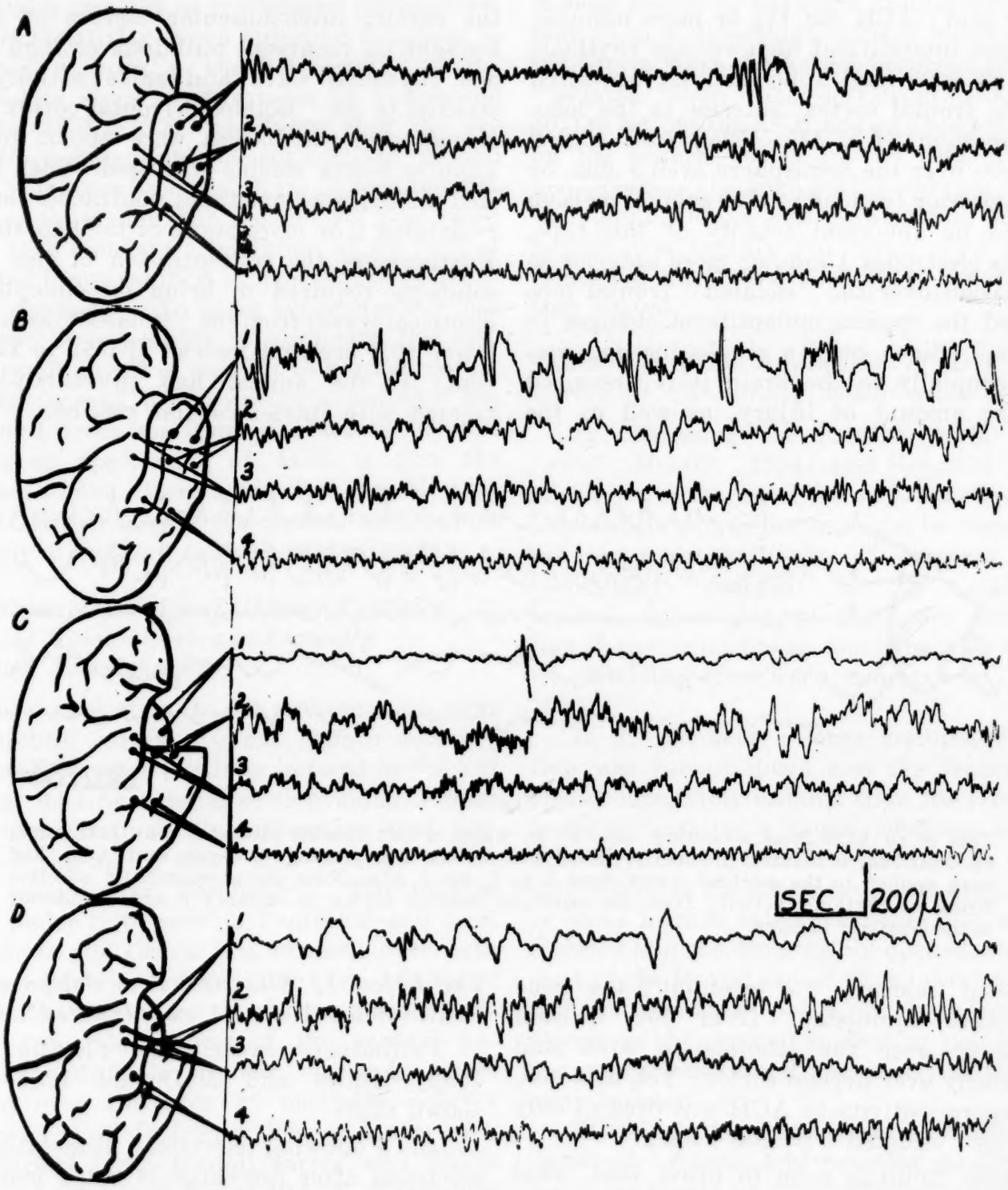

Fig. 12

ECG from a patient with epileptic seizures that clinically apparently arose in the anterior right temporal lobe.

A shows the ECG of the resting activity obtained shortly after opening the dura mater.

B single acute subpial lobotomy incision has been made in the temporal lobe along the dotted line. Note the activation of the spiking from the anterior temporal lobe a few minutes after its partial isolation.

C ECG following excision of the anterior 4 cm of the temporal lobe.

D the same following removal of about 1 more cm of temporal lobe. Some abnormality is still recorded from the Island of Reil.

jections of ACH and also the topical application of GABA (Gamma amino butyric acid 1 per cent) may cause discharges of wave and spike electrical activity selectively from chronically "isolated" areas of cerebral grey matter.

The Effect of Neuronal Isolation on a Temporal Lobe Epileptogenic Focus in Humans

In 2 human patients with clinical temporal lobe epilepsy and an electrical "epileptogenic" focus in the anterior temporal lobe, the anterior 5 cm. of the temporal lobe was largely isolated from the remaining brain by means of a single subpial lobotomy incision. EEGs taken before making the subpial incision revealed random spike activity over the anterior portion of the temporal lobe (fig. 12A). Immediatley after performing the lobotomy incision there was a marked increase in the voltage and amount of the spike activity recorded from the anterior temporal lobe (fig. 12B), indicating an activation of the "epileptogenic" electrical focus following partial isolation. The anterior 5 cm. of the temporal lobe and the temporal lobe "focus" was then largely excised.

The Origin of Focal Slow Waves in the Electroencephalograms of Patients with Brain Tumors

In 5 patients with gliomas involving one cerebral hemisphere, EEG's were obtained pre-operatively and electrocorticograms at the time of operation. In the EEG's focal slow waves at 1 to 2 or more per second were recorded from the neighborhood of the tumor. At operation characteristic electrical bursting of the type which occurs from cerebral cortex following neuronal isolation was recorded from the partially isolated cerebral cortex overlying, or immediately surrounding the tumor, both through the dura and also with electrodes directly on the cortex (fig. 13). The bursting in the ECG was manifested in the EEG as slow waves and it is again suggested (Echlin *et al.* 1952) that the origin of at least some of these slow waves around brain tumors is the result of the "isolation" of cortical neurones.

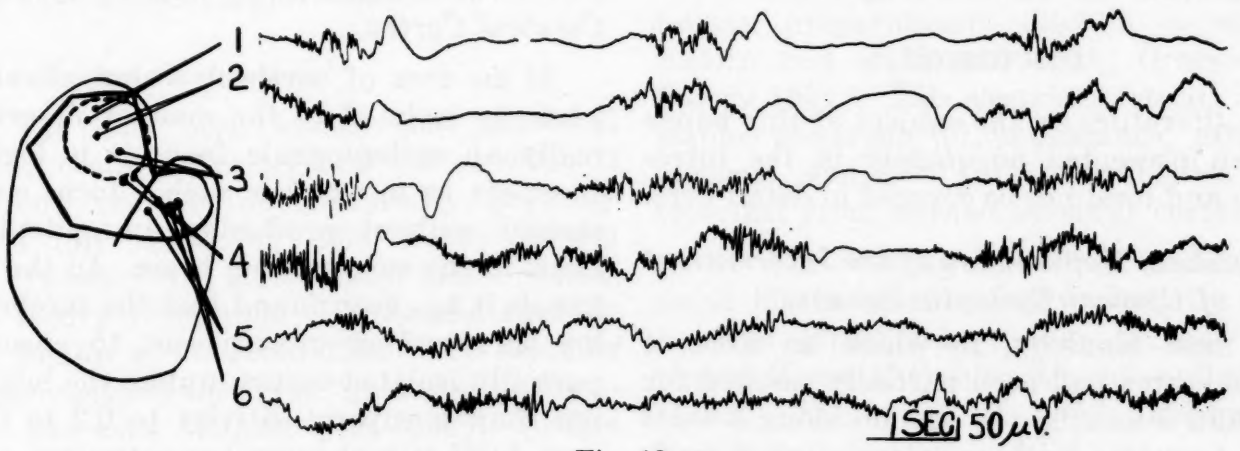

Fig. 13

This is an ECG from the cerebral cortex of a human patient B. with a subcortical frontal lobe brain tumor (glioma) outlined by dots. Note the typical bursting in channels 1, 2, 3 and 4 which are recording from the partially isolated cortex (undercut by tumor) directly over the tumor. Channels 5 and 6 are from the temporal lobe and show no bursting. The individual bursts in the ECG were recorded in the EEG as 1 to 2 per sec. waves. This figure illustrates that the bursts in the ECG (and apparently the slow waves in the EEG) are the result of the partial isolation of cortical nerve cells.

The Electroencephalogram from Monkeys with an Area of Chronically Isolated or Partially Isolated Cerebral Cortex

Electroencephalograms were obtained from more than half of the 90 animals in which an

area of cerebral cortex had been chronically "isolated". Only 5 per cent of these monkeys developed known clinical seizures. No significant abnormalities were noted in the EEGs. The electrical activity appeared essentially symmetrical from the two hemispheres, even when driven by photic stimulation. This did not seem surprising when one considers that high amplitude rhythmic spike discharges were frequently recorded from one gyrus and only low voltage activity from a neighboring gyrus a few millimeters away. In other words, focal epileptiform, or other abnormal cortical electrical firing from "isolated" cortex, was usually overshadowed in the EEG by the larger potential changes, both subcortical and cortical, from the surrounding brain.

DISCUSSION

The literature on the subject of this paper has been presented adequately in the introduction and need not be covered in detail here.

A Theoretical Explanation of the Intermittent Nature of Clinical Epileptic Seizures

In most monkeys, in which an area of cerebral cortex had been partially isolated for more than 6 months (by section along 3 sides and undercutting), there was a marked tendency for the high voltage epileptiform electrical activity, precipitated by the wide topical application of acetylcholine, to remain within the confines of the partially isolated zone. Certainly if a rhythmic epileptiform discharge of such high amplitude were precipitated in normal cortex by local electrical stimulation it should spread at least a short distance through the deeper layers of the grey matter, as demonstrated by Adrian (1936) and Burns (1951) and into contiguous areas of cortex (Erikson 1940). In the present experiments it was as though there existed, or had developed, an inhibitory factor or mechanism which tended to confine the abnormal focal electrical discharge within the pathological (partially isolated) area of cortex where it originated. If chronic partially isolated cerebral cortex is really epileptogenic cortex then the important factor in precipitating an individual epileptic seizure is apparently not only the excessive nature of the focal discharge, as commonly postulated, but the temporary breakdown of an inhibitory mechanism which most of the time (in the chronic preparation, or epileptic patient) prevents the discharge from spreading. In the present experiments eserine used topically or intra-muscularly followed by the topical use of acetylcholine was usually sufficient to overcome this proposed inhibitory mechanism; for then the epileptiform electrical discharge generally did spread through the open unsevered end of the isolated zone and caused clonic convulsive movements.

The Surgical Excision of "Epileptogenic" Cerebral Cortex

If an area of cerebral cortex, chronically partially isolated in the manner described is really an epileptogenic focus it is logical to speculate as to whether such a focus could be excised without producing an epileptogenic focus in the surrounding brain. In the experiments it has been found that the cerebral cortex surrounding or adjacent to chronically partially isolated cortex, unlike the latter, did not show a supersensitivity to 0.2 to 0.5 per cent ACH nor abnormal spontaneous spiking or bursting, presumably because there was quantitatively only a mild degree of isolation of the neurones in this surrounding grey matter. Therefore, if the partially isolated supersensitive cortex could be excised, or removed by suction, subpially (as performed by Penfield) without damaging the blood supply, it is logical to assume that no further change in the sensitivity, or in the ECG, should occur in the surrounding cerebral cortex. This concept is in keeping with the observation that surgical removal of an "epileptogenic focus" may be curative(Penfield and Jasper 1954).

Some Possible Clinical Effects of Isolation

The fact that nerve cells in the brain show an increased sensitivity to many stimuli when they have been chronically "isolated" may

be of clinical significance whether or not this factor is important in the production of epilepsy. Such a supersensitivity of nerve cells might explain some of the clinical changes that follow lobotomy for mental illness (Echlin 1956). In paralysis agitans a similar sensitivity of cells in the globus pallidus, or ventro-lateral nucleus of the thalamus, might develop as a result of their partial isolation by a chronic encephalitic process. In fact, any relatively large brain injury may cause some change in the sensitivity of neurones at a distance and over wide areas to certain chemical stimulating agents (Stavraky 1943, 1946; Fisher and Stavraky 1944; Ward 1953; Echlin 1954; Spiegel and Szekely 1955) and this might have clinical significance.

The "Isolation Phenomena"

It has long been known that electrical bursting occurs from cerebral cortex when it is acutely isolated, or chronically partially isolated (Bremer 1935, 1936, 1938; Spiegel 1937; Swank 1949; Kristiansen and Courtois 1949; Henry 1949, 1950; Henry and Scoville 1952; Echlin *et al.* 1950, 1952). To describe this phenomenon the term "isolation phenomenon" was used (Echlin *et al* 1952). To this characteristic of the "isolated" cortex may be added the phenomenon of supersensitivity to acetylcholine and other stimuli in chronic preparations (Echlin 1954; Echlin and McDonald 1954; Spiegel and Szekely 1955).

The two "isolation phenomena" of bursting and of supersensitivity are apparently quite different in the mechanism of their production, although "isolation" is the factor that brings both of them on. The phenomenon of bursting comes on immediately after isolation and may persist for at least 3½ years. It cannot be the result of denervation in the sense of Cannon for, of course, no degeneration of nerve fibres would have occurred in acute preparations. On the other hand, the supersensitivity of chronically "isolated" cortex to topically applied acetylcholine does come on gradually and may be the result of denervation as postulated in Cannon's Law (Cannon and Rosenbleuth 1949).

SUMMARY AND CONCLUSIONS

1. A technique is described of neuronally isolating an area of cerebral cortex through small stab wounds in the dura mater. This method, a modification of that described by Kristiansen and Courtois 1949, has largely avoided the formation of subdural adhesions and has made it possible to obtain electrocorticograms, in 100 monkeys and 3 humans, at a second operation 2 weeks to 3½ years later, with little injury to the cerebral cortex or pial circulation.

2. "Spontaneous" electrical activity was present in chronic completely neuronally isolated cerebral cortex provided the circulation was adequately maintained (20 monkeys and 2 human preparations) (Echlin *et al.* 1952; Echlin and McDonald 1954; Grafstein and Sastry 1957). This electrical activity was unstable, abnormal in appearance, often paroxysmal, and bore little resemblance to that recorded from normal cerebral cortex.

3. The resting electrical activity from small blocks of chronically partially isolated cerebral cortex was similar to that usually regarded as characteristic of epileptogenic cortex (Echlin *et al.* 1952; Echlin 1953; Echlin and McDonald 1954).

4. The nerve cells in areas of chronically "isolated" frontal or parietal cerebral cortex became supersensitive to topically applied acetylcholine (Echlin 1954; Echlin and McDonald 1954; Spiegel and Szekely 1955), eserine and electrical stimulation. The topical application of acetylcholine 0.2 to 0.5 per cent widely to the cerebral cortex in such chronic preparations precipitated discharges of rhythmic wave and spike epileptiform electrical activity selectively from the "isolated" area in 90 per cent of the 80 animals and in the 1 human studied. The local use of 1 per cent acetylcholine or of 1 per cent eserine followed by 0.2 to 1 per cent ACH resulted in a spread of the epileptiform rhythmic potentials from the partially isolated zone to the motor cortex and clonic seizures and, less often, generalized electrical and clinical convulsions.

5. In contrast to these findings 0.2 to 0.5 per cent acetylcholine never caused epileptiform electrical discharges when applied topically to the unanesthetized frontal or anterior parietal cortex of normal monkeys (9 preparations) or to the hemisphere homologous to one containing a chronically ''isolated'' block of grey matter (10 preparations).

6. Evidence is provided that the ''isolation factor'' rather than injury or ischemia is the important factor in the causation of the supersensitivity of chronically neuronally ''isolated'' cerebral cortex (Echlin 1956).

7. Characteristic bursting was present in electrocorticograms from the partially isolated cerebral cortex overlying and surfounding brain tumors. The bursts appeared in the EEG as slow waves. It is again suggested that at least some of the slow waves in the EEG from around brain tumors are the result of the partial isolation of cerebral neurones (Echlin *et al.* 1952).

8. Acute surgical ''isolation'' of a temporal lobe spike focus in an epileptic patient caused an activation of the electrical focus.

9. It has been demonstrated that chronic partially isolated human or monkey cerebral cortex has many properties, characteristics and reactions commonly regarded as characteristic of epileptogenic cortex. It therefore seems probable that chronic partial isolation of cerebral neurones by scar tissue, brain tumor, or other pathology, is an important factor — if not the basic factor — in the causation of focal epilepsy.

RÉSUMÉ

1. On décrit une technique d'isolement neuronal d'une aire de cortex cérébral, à travers des petites plaies ponctiformes de la duremère. Grâce à cette méthode on a pu éviter largement la formation d'adhérences sous-durales, et il est devenu possible d'obtenir des électrocorticogrammes chez 100 singes et chez trois humains, à une deuxième intervention ayant lieu de deux semaines à 3½ ans plus tard, avec très peu de lésion au cortex cérébral ou à la circulation pie-mèrienne.

2. L'activité électrique « spontanée » était présente dans le cortex cérébral complètement isolé neuronalement pendant 2 semaines à 3½ ans, à condition que la circulation soit maintenue de façon adéquate (20 singes et 2 préparations humaines). Cette activité électrique était instable, d'apparence anormale, souvent paroxystique, et ressemblait très peu à celle enregistrée dans du cortex cérébral normal.

3. L'activité électrique de repos à partir de cortex cérébral partiellement et chroniquement isolé ressemblait à celle qui est habituellement considérée comme étant caractéristique de cortex épileptogène.

4. Les cellules nerveuses dans des aires frontales ou pariétales de cortex cérébral chroniquement « isolé » sont devenues sursensibles à l'acétylcholine appliqué topiquement, à l'éserine, et à la stimulation électrique. L'application topique d'acétylcholine 0.2 à 0.5 pour cent sur des zones étendues de cortex cérébral dans de pareilles préparations chroniques, a précipité des décharges rythmiques d'activité électrique épileptiforme de pointe-ondes de façon sélective à partir de l'aire « isolée » dans 90 pour cent des 80 animaux et dans le seul humain étudiés. L'emploi local d'acétylcholine 1 pour cent ou d'éserine 1 pour cent suivi d'acétylcholine 0.2 à 1 pour cent donnait une propagation des potentiels rythmiques épileptiformes à partir de la zone partiellement isolée vers le cortex moteur, et des crises cloniques, et, moins souvent, des convulsions généralisées électriques et cliniques.

5. En contraste avec ces trouvailles l'acétylcholine 0.2 à 5 pour cent n'a jamais produit des décharges électriques épileptiformes lorsqu'il était appliqué topiquement au cortex frontal ou pariétal non-anesthésié de singes normaux (9 préparations), ou à l'hémisphère homologue à celui contenant un bloc de substance grise chroniquement « isolée » (10 préparations).

6. On fournit la preuve que c'est « l'isolement » plutôt que la lésion ou l'ischémie qui est le facteur important dans la pathogénie de la sursensibilité du cortex cérébral chroniquement « isolé » neuronalement.

7. Des bouffées caractéristiques étaient présentes dans des électrocorticogrammes à partir du cortex cérébral partiellement isolé

superposé à, ou entourant, des tumeurs cérébrales. Les bouffées paraissaient dans l'EEG sous forme d'ondes lentes. On suggère de nouveau qu'au moins quelques-unes des ondes lentes dans l'EEG de l'alentour des tumeurs cérébrales soient le résultat de l'isolement partiel des neurones cérébraux (Echlin *et al.* 1952).

8. « L'isolement » chirurgical aigu d'un foyer de pointes du lobe temporal chez un malade épileptique a produit l'activation du foyer électrique.

9. On a démontré que le cortex cérébral humain ou du singe, chroniquement et partiellement isolé, a de nombreuses propriétés, caractéristiques ou réactions, considérées généralement comme étant caractéristiques de cortex épileptogène. Il paraît donc probable que l'isolement partiel chronique des neurones cérébraux par du tissu cicatriciel, par une tumeur cérébrale, ou par une autre pathologie, soit un facteur important — si non le facteur de base — dans la pathogénie de l'épilepsie focale.

ZUSAMMENFASSUNG

1. Eine Technik, wird beschrieben um neuronal isolierte Rindenterritorien durch kleine, penetrierende Verletzungen der Dura mater herzustellen. Mit dieser Methode kann die Ausbildung von subduralen Adhäsionen im allgemeinen verhütet werden, und dies ermöglichte es während einer zweiten Operation, welche innerhalb einer Zeitspanne von 2 Wochen bis 3½ Jahre nach der ersten Intervention ausgeführt wurde, Elektrocorticogramme bei 100 Affen und 3 Patienten, aufzunehmen. Die Hirnrinde und die Blutzirkulation in der Pia wurde nur einem minimalen Insult ausgesetzt wurden.

2. « Spontane » elektrische Aktivität konnte für eine Periode von 2 Wochen bis 3½ Jahren in Rindengebieten festgestellt werden, welche vollständig neuronal isoliert waren vorausgesetzt dass die Blutzirkulation in adäquater Weise erhalten blieb (20 Affen und 2 Patienten). Diese elektrische Aktivität war unstabil, abnorm in ihrem Auftreten, oft paroxysmal, und zeigte nur eine entfernte Ähnlichkeit mit derjenigen der normalen Hirnrinde.

3. Die Ruheaktivität kortikaler Gebiete, welche partiell isoliert waren, zeigte im chronischen Experiment die Charakteristika, welche im allgemeinen als typisch für diejenige eines kortikalen Krampffokus betrachtet werden.

4. Die Nervenzellen in chronisch « isolierten » frontalen und parietalen Rindengebieten erwiesen sich als überempfindlich gegenüber örtlich appliziertem Azetylcholin, Eserin und lokaler elektrischer Reizung. Die lokale Applikation von 0.2 bis 0.5-prozentigen Azetylcholin über ein grosses Hirnrindengebiet, löste in 90 Prozent der 80 Versuchstiere und in 1 Patienten rhythmische ''spike and wave'' Entladungen epileptiformen Charakters aus, welche selektiv in der ''isolierten'' Rindengegend auftraten. Die lokale Applikation von einprozentigem Azetylcholin oder von einprozentigem Eserine mit nachfolgender Applikation von 0.2 bis einprozentigem Azetylcholin führte zu einer Propagation der epileptischen rhytmischen Entladungen von einer partiell isolierten Zone in die motorische Rinde, und klonische Krämpfe oder, weniger häufig, generalisierte elektrische und klinische Konvulsionen wurden auf diese Art ausgelöst.

5. Im Kontrast zu diesen Befunden ist zu bemerken, dass 0.2 bis 0.5 prozentiges Azetylcholin nie epileptiforme elektrische Entladungen hervorrief, wenn es örtlich auf die unnarkotisierte frontale oder parietale Hirnrinde von normalen Affen (9 Versuchstiere) oder auf eine Hemisphäre appliziert wurde, welche homolog derjenigen war, welche einen chronisch « isolierten » Block grauer Substanz enthielt (10 Versuchstiere).

6. Indizien werden angegeben, welche darauf hindeuten, dass die « Isolierung » an sich eher als die Verletzung oder Ischämie der entscheidende kausale Faktor für die Ausbildung der Ueberempfindlichkeit des chronisch neuronal ''isolierten'' Kortex darstellt.

7. Charakteristische, gruppierte Entladungen wurden in Elektrocorticogrammen von partiell isoliertem Kortex festegestellt, welcher über oder nahe bei einem Gehirntumor lag.

Diese gruppierten Entladungen erschienen im EEG als langsame Wellen. Es wird vermutet, dass wenigstens gewisse langsame Wellen im EEG, welche in der Nähe von Gehirntumoren auftreten, als das Resultat einer partiellen Isolierung von Rindenneuronen betrachtet werden müssen (Echlin *et al.* 1952).

8. Bei einem Epileptiker wurde ein Schläfenlappenfokus, welcher Spitzenentladungen produzierte, akut chirurgisch "isoliert", und dies führte zu einer Aktivierung des elektrischen Herdes.

9. Es wurde gezeigt, dass chronisch partiell isolierte Rindengebiete beim Menschen und beim Affen manche Eigenschaften und Reaktionen aufweisen, welche im allgemeinen als charakteristisch für epileptogenen Kortex betrachtet werden. Es scheint daher als wahrscheinlich, dass chronische partielle Isolierung zerebraler Neurone durch Narbengewebe, Gehirntumoren oder durch andere pathologische Prozesse, einen wichtigen Faktor und vielleicht sogar den entscheidenden Faktor darstellt, welcher dem Auftreten herdförmiger, epileptischer Entladungen zugrunde liegt.

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THE ELECTROENCEPHALOGRAM IN PARKINSON'S SYNDROME [1]

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James Parkinson in his classical essay "On the Shaking Palsy" in 1817 commented therein on the extreme regularity of the to and fro resting tremor seen in his 5 reported cases. Kinnier Wilson (1925) in his Croonian lectures, and Hoefer in 1940 postulated central tremor centers to account for the bilateral synchrony of this tremor; its arrest with voluntary motor movement; its augmentation when under stress and disappearance with sleep. In 1938, one of us (R.S.S.) with Stanley Cobb investigated 37 patients with Parkinson's disease to determine if any reflection of this regular 4 to 5 per sec. tremor could be seen in the scalp EEG tracings. In patients with strong tremors, movement artefacts in the scalp EEG were noted to be synchronous with the tremor. When relaxed such patients had considerably less shaking and the EEG lost this movement artefact and showed a normal pattern on both sides. Electromyographic tracings of the tremor at the same time as the electroencephalogram further identified scalp discharges as pure artefact. In our small series 34 normal records were found, 3 borderline and 1 mildly abnormal with 6 and 7 per sec. slow waves bilaterally. As a result of this study it was believed that the electroencephalogram was generally normal in Parkinson's syndrome.

In recent years, however, there has been much more critical attention directed to this disease from several points of view. There has been some successful production of tremor, rigidity, and other features of the condition in monkeys by means of stereotaxically placed lesions (Schreiner *et al.* 1958). In such preparations both electroencephalogram-depth and electromyographic tracings have been made. Neurosurgeons, notably Russell Meyer (1958), Irving Cooper (1956) and Wycis (1958) have used stereotaxic guides to place lesions in such deep structures as the globus pallidus, thalamus, and even midbrain structures, recording from such areas and following the specific effects of such lesions on alleviation of tremor, rigidity and other symptoms.

With our own Parkinson Clinic in its tenth year we found as the number of patients increased more and more exceptions to the concept that the electroencephalogram in this disorder was within normal limits. Furthermore, when we began to refer our own patients for neurosurgical intervention we began to look for laboratory tests that might lead to better selection of suitable ones for this procedure. In 1957 we began to collect a new series of electroencephalograms in this disease to see what new factors were bringing in so many that were abnormal.

METHODS

Electroencephalograms were taken on an 8 or 16 channel Grass or on the 15 channel Alvar. The routine placements of our laboratory (see fig. 4B) which are similar to the International placements were used. Hyperventilation and stroboscopic activation with single, paired, and 5, 10, 15 and 20 flashes per sec. were used routinely. The patients came from the Parkinson Clinic, and private and ward in-patients and now and then from office visits as well.

Whenever a tremor artefact presented itself additional leads were run to surface electrodes over the muscles of the forearm and

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recorded as the electroencephalogram was taken. With close observation during recording, however, it ordinarily was easy to see an overt tremor of the head as it was registering on the paper so the artefact so produced could be indicated. The abnormalities we describe appear to be quite distinct from this obvious movement artefact.

In most of the examinations the patient had been off his usual medication for 36 to 48 hours. (We wanted a drug-free baseline for this and other tests for the purpose of evaluating therapy.) In a few cases it was not wise or feasible to withdraw the medication. Furthermore, we could see no difference in the EEG tracing of patients on or off the usual anticholinergic drugs we were using such as Artane, Benadryl, Kemadrin, Parsidol, etc. There were, however, three situations where overdosage of drugs produced marked toxic confusional states. In these three (one from Hyoscine, one from Benadryl, and one from Parsidol) there were slow waves bilaterally which disappeared when the drug was withdrawn leaving the electroencephalogram normal.

The subdivision of Parkinson's disease into post-encephalitic, arteriosclerotic, and idiopathic types seems to us to have little clinical significance. Of the 75 patients in this EEG survey only 3 had a definite history of encephalitis in the past, and less than half recalled any illness during the influenza epidemic 1917-1925. Cerebral arteriosclerosis is an unproved etiological agent since many patients develop their first symptoms well before any demonstrable signs of vascular disease exist. There are countless examples of diffuse and severe cases of cerebral vascular disease without any evidence of Parkinson's disease. We have not seen any patient whose symptoms could be ascribed to tumor or trauma of the brain although there are such relationships described in the literature.

It might be helpful to define Parkinson's syndrome as a motor disorder with the following 9 components:

1. Reduction or loss of semi-automatic associated muscle movements such as arm swinging in walking, spontaneous blinking of eyes, animated facial movements with speech and attention.

2. Passive rigidity of muscles particularly at the wrist or elbow joint of cog-wheel type.

3. Rhythmic regular 4 to 6 per sec. tremor especially of the fingers when the limb is at rest.

4. Loss of dexterity in fine finger movements and in coordinated movements involving simultaneous use of different muscle groups (reaching into pocket while rising from a chair).

5. Insidious steady or rapid progression over the years without specific remissions.

6. Exacerbation of the first four when under stress.

7. Improvement of the first four when rested, relaxed or asleep.

8. Akinesia, defined as a reduction or loss of ability to initiate and maintain simple or complicated motor acts such as walking, talking, writing and dressing.

9. Loss of organizational planning and occupational ability with depression of responsibility, mood, ambition and independence.

The so-called classical concept of Parkinson's disease embraces various combinations of 1 through 7, i.e. is essentially a syndrome of rigidity-tremor symptoms. The symptoms under 8 and 9 are common enough in advanced cases to be noted by most clinicians but frequently are absent or minimal in the others, at least for many years. In general, as patients continue to progress into severe bilaterally involved cases more and more of 8 and 9 become factors in their disability. The nature of these so-called "mental signs" included in category 9 is different from those ordinarily associated with senility and diffuse cerebral vascular disease. Patients are clearly oriented as to both space and time, comprehension and understanding of information brought to their attention either by writing or conversation is not significantly impaired. Indeed if one takes the time and the patience it is not impossible to establish legal competence from the standpoint of making a will. With the loss of facial expression, stooped posture, drooling of saliva, and their sessile almost catatonic fixed pos-

tures, they give the appearance of a severe dementia. Due to the item of akinesia they do not participate in any kind of social contact either conversational or motor. They appear totally indifferent. In most instances they allow relatives or nurses to do everything for them without any feeling of embarrassment or irritation. Curiously, many require their entire meal to be fed to them, swallowing it slowly, but completely, but frequently showing lapses in adequate chewing. On the other hand, they can be instructed and urged to feed other patients food in a surprisingly efficient manner. They show varying amounts of real depression of mood and frequently will cry spontaneously when efforts are made to encourage them. Such severely obtunded patients in sudden emergencies have been known to leap out of their beds and even run down the stairs, carrying a child in their arms, if the house was afire.

The clinical impression one gets after much contact with such individuals is that the input signals from their environment are coming in without too much impairment, and the difficulty is in some ill-defined blocking of appropriate and adequate responses of a motor type to the usual incoming signals. As a result of these two components, 8 and 9, such patients are tremendously handicapped and helpless. They fall into severe invalid states requiring nearly continuous care and help throughout the day. Ordinary single simple motor reaction time determinations are not greatly prolonged in spite of this severe and generalized motor deficit, reaching values of .24 sec. (Schwab 1958). Recent observations, however, in a present study show gross impairment in multiple choice reaction time determinations. Ordinary I.Q. determinations which are frequently based on participation with numerous motor acts show extraordinary levels of deterioration which are at extreme variance with the vocabulary levels obtained.

In sharp contrast to the above, patients with severe bilateral tremor and/or marked rigidity are frequently able to be completely independent throughout the day even though they must exert tremendous efforts to do their ordinary tasks alone and without help. Such individuals who have the necessary drive to be thus independent may take four or five times as long to dress as a normal person requiring intense concentration to complete the task. They only become hopelessly inefficient and helpless when they are under unusual stress or have to hurry to complete chores within a normal period of time.

One might subdivide the syndrome into an X-type (rigidity and tremor types without the 8 and 9 signs) and a Y-type with 8 and 9 signs early in the disease, with tremor and rigidity of secondary importance. In the Y-type, however, *all* of the other elements are usually fully present. The clinical picture is so typical that question of diagnosis is never a problem.

RESULTS

Electroencephalographic abnormalities

As may be seen in figure 1, of 75 patients tested there appear 36 (48 per cent) normal tracings and 39 (52 per cent) abnormal ones. The latter may be subdivided into mildly, 6 (8 per cent), moderately, 14 (19 per cent), and markedly, 16 (21 per cent) abnormal. The abnormalities were:

random diffuse theta and delta activity	11
random theta and delta activity in the posterior regions only	16
random theta and delta slowing on the right side only	3
random theta and delta slowing on the left side only	4
random diffuse theta and delta activity but with left side more abnormal	4
random diffuse theta and delta activity but with right side more abnormal	2

Correlation with age and with duration of disease

Figure 2 represents an analysis of normal and abnormal tracings by decades. It is evident that the normal and abnormal tracings occur similarly, and the range of both very closely approximates the age curve for the Parkinson syndrome patients attending clinic,

as previously reported by Schwab, Doshay, Garland, Bradshaw, Garvey and Crawford (1956). There is a slight but insignificant increase in the abnormal EEGs in patients over 60 years of age.

Figure 3 represents the normal and abnormal tracings as broken down by the duration of the disease. Again there is no difference between the patients with normal and those with abnormal electroencephalograms.

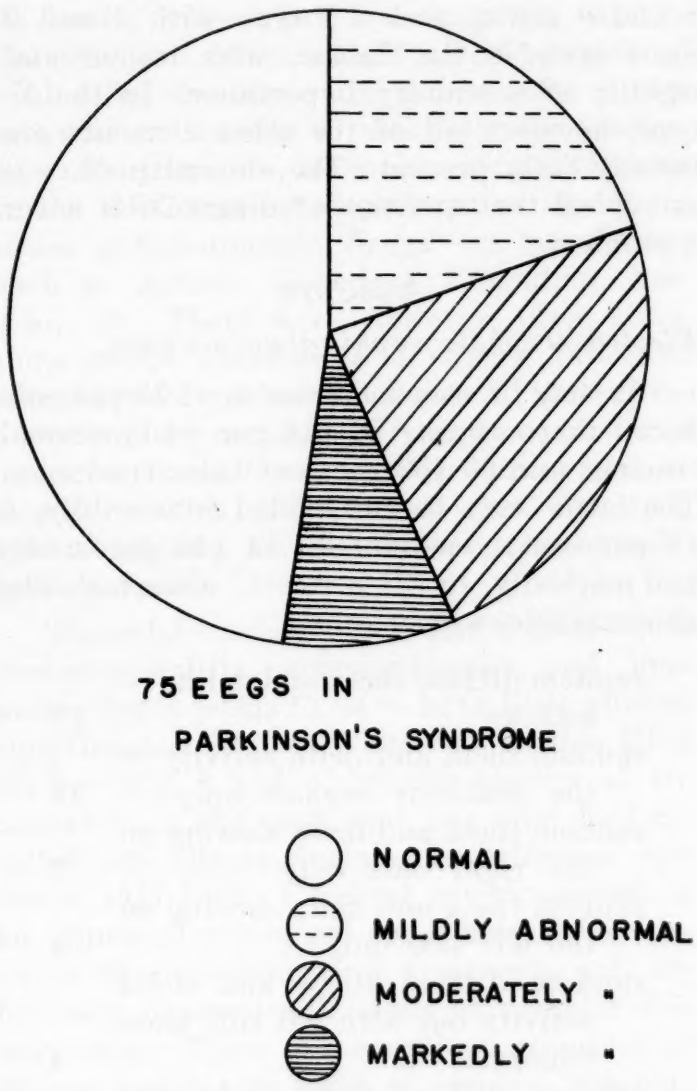


Fig. 1
A breakdown of the EEGs in 75 patients with parkinsonism seen in the year 1957.

Deterioration of the EEG in Parkinson's syndrome

Up to the present time examples of this have been uncommon in our clinical material since routine EEG study was not a part of the investigation of Parkinsonian patients. It has been observed, however, four times. Our best documented case is as follows:

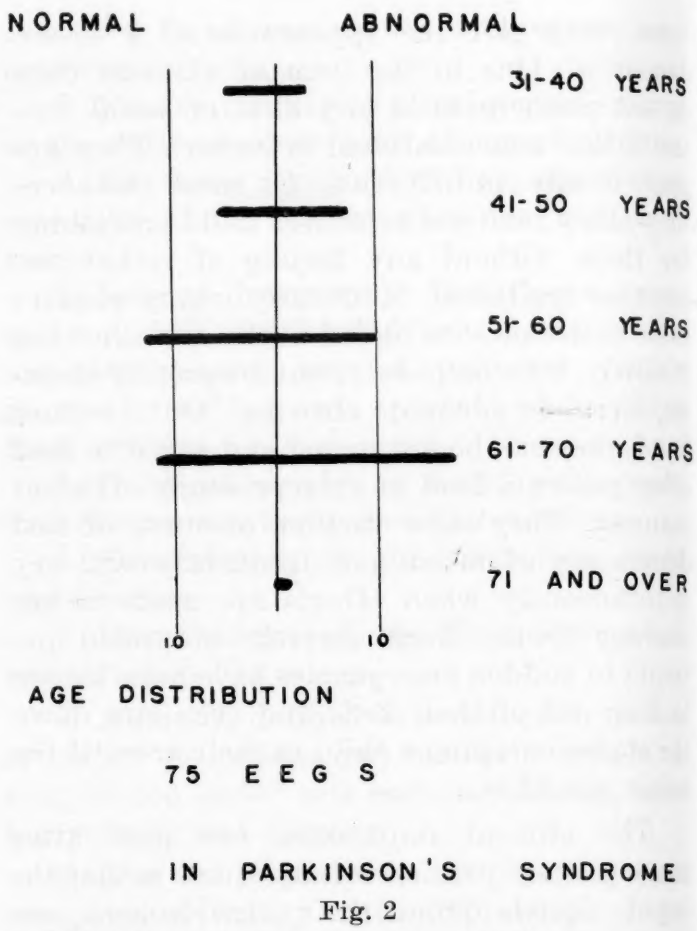


Fig. 2
Distribution of age in decades in relation to the normal or abnormal EEG findings.

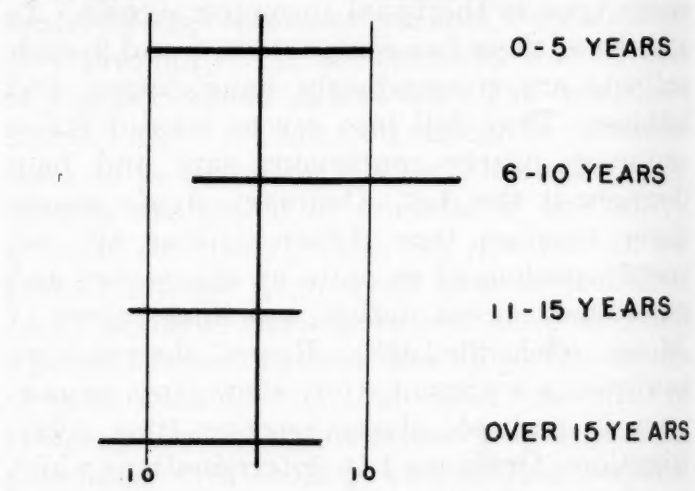
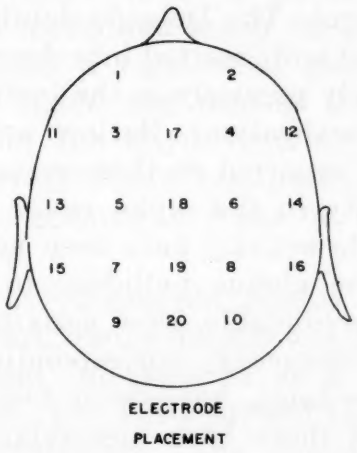
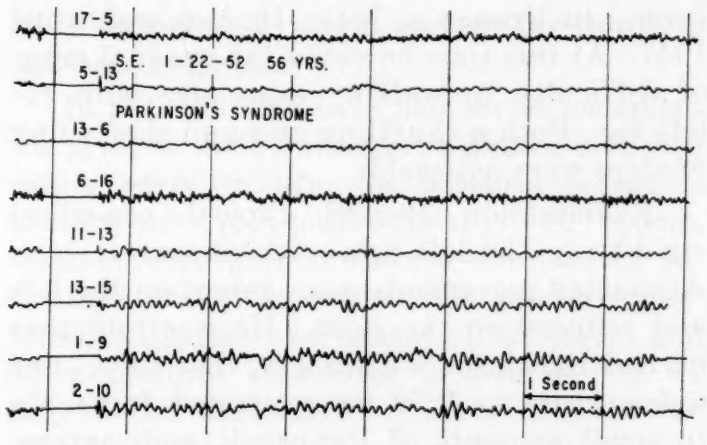
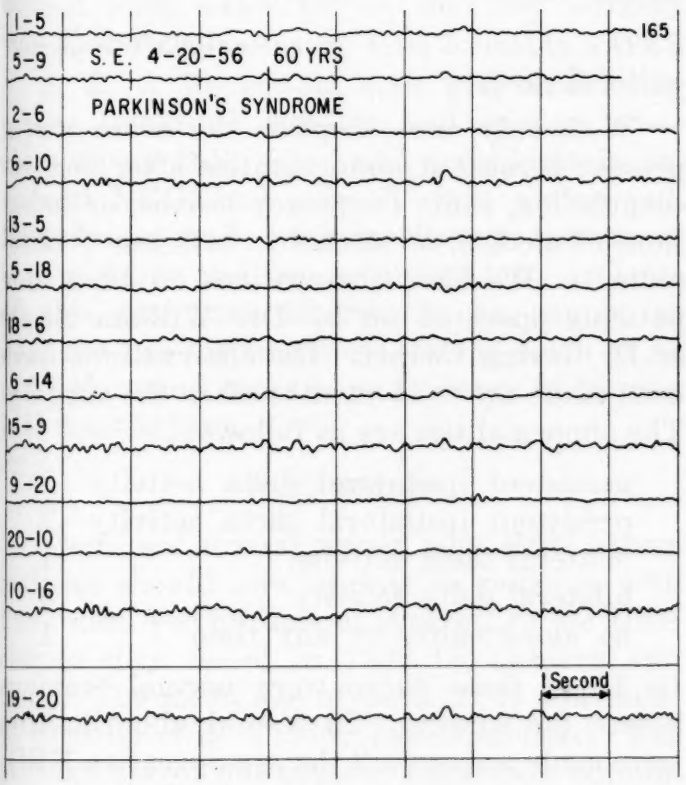


Fig. 3
Distribution of the normal and abnormal EEGs in relation to the duration of the illness in 5-year periods.







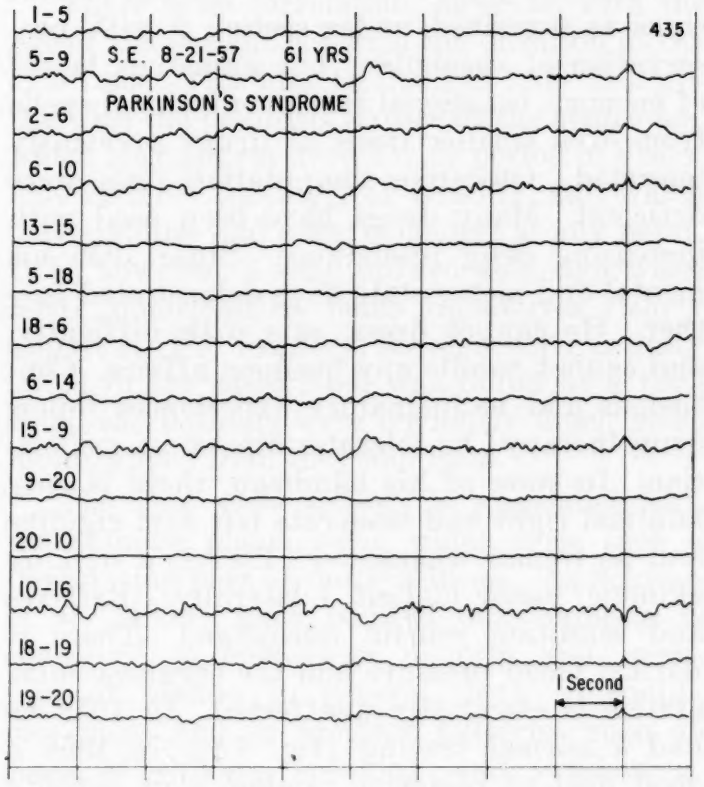


Fig. 4

An example of the slow change from normal to abnormal in a patient with Parkinson's disease over a 5-year period.
Upper left are the electrode placements and numbers used.
Upper right is the tracing of 1952.
Lower left is the tracing of 1956.
Lower right is the tracing of 1957.
Patient was off medication in all these examples.

S. E. A 62-year-old, retired business man had a severe case of influenza or "trench fever" in France in 1918. He was well until 1947. At this time he noted the gradual onset of difficulty in walking especially with his left leg. Both a shuffling gait and shortening of steps were noticeable.

Examination showed typical cog-wheel rigidity in the left arm without any tremor. Associated movements were absent on the left and reduced on the right. He was told that he had Parkinson's disease at that time. For a few years to 1952 he responded favorably to small amounts of Panparnit and Artane. Gradually he was forced to stop playing golf, tennis and squash which had been his favorite recreation. By 1955 there were marked mental signs as described under section 9 with preservation of vocabulary but numerous lapses of memory, occasional frank confusional spells from even smaller doses of drugs previously tolerated. Objective computation tests were deficient. Many drugs have been used with increasing drug intolerance. Since 1955 his mental and motor state have deteriorated further. He cannot dress, eats with difficulty, and cannot handle any business affairs. Confusions and hallucinatory experiences follow drug therapy; he tolerates almost no medication. In spite of his handicap, there is only minimal right and moderate left arm rigidity and no tremor whatsoever. He has a striking akinetic motor deficit bilaterally. Reflexes and sensation remain unchanged. There is normal blood pressure and the cardiovascular system is essentially unaffected. In 1952 he had a normal tracing (fig. 4A), in 1956 a good deal of posterior random slow activity (fig. 4C), in 1957 the posterior theta and delta activity was even more prominent (fig. 4D).

EEG's in depth recording in Parkinson's syndrome

Recent neurosurgical procedures to control tremor and rigidity in Parkinson's syndrome have been carried out at the Massachusetts General Hospital by Dr. William Sweet, to whom we are indebted for our observations. Such procedures have been directed towards the mesial aspect of the globus pallidus, using the stereotactic apparatus under both pneumographic and routine roentgenographic control. The Delgado depth electrode was employed and inserted into the globus pallidus as nearly precisely as the instrument allows such localization. Barlow and Brazier (1957) have reported on these recordings. At times, activity in the alpha range and occasionally, delta activity have been noted in the region of the globus pallidus; in other instances, unpredictable, slow activity of theta and delta frequency, corresponding to the surface recordings, have been noted. In no instance has there been any relationship of these rhythms with the tremor recorded simultaneously as an electromyogram (Bravo and Cooper 1956).

EEG's observed post-operatively after globus pallidus surgery

With only one exception the brain waves present persistent abnormalities after electrocoagulation, radio frequency lesions, or injections of alcohol, or alcohol in cellulose ("Etopalin"). We have observations on 16 of our patients operated on by Dr. William Sweet or Dr. Irving Cooper. The observations have been made up to 15 months after the surgery. The abnormalities are as follows:

persistent ipsilateral delta activity	9
persistent ipsilateral theta activity	2
bilateral theta activity	1
bilateral delta activity	3
no abnormality at any time	1

In 12 of these there were normal tracings before the surgery. In 2 mild abnormalities were made worse. In 2 the pre-operative EEGs were quite abnormal and remained clearly and diffusely abnormal throughout the post-operative follow up. In both of these the surgical results were poor.

F. A. A 57-year-old physician developed Parkinson's disease 20 years previously. He tolerated drugs well and was able to continue his work until 1954. From then on symptoms of akinesia, marked difficulty with speech and some with swallowing, developed. He could no longer tolerate any of the solanaceous drugs previously useful. Even when off drugs there were periods of nocturnal confusion.

The rigidity and tremor were strongly present bilaterally. In 1956 his EEG showed some delta waves and much theta bilaterally. In July 1956 a right-sided globus pallidus lesion was made and during the procedure dilatation of the third ventricle was noted. A post-operative left hemiparesis developed and in the ensuing 2 years he has steadily deteriorated.

M. B. A 62-year-old female with severe bilateral Parkinson's disease was admitted for neurosurgical intervention as a measure of desperation. The EEG showed bilateral moderate abnormalities. The pre-operative air study produced such an increase in her akinesia, lack of responsiveness and, in general, caused such exacerbation that the surgery was abandoned.

S. R. A 59-year-old male with moderately severe left-sided rigidity and tremor, some akinesia on both sides, and a moderately abnormal EEG, had a small right globus pallidus lesion made with excellent reduction of both rigidity and tremor on the left. In spite of this one year afterwards he cannot or does not use his freed left side as much as he did before and there is no evidence of pyramidal tract injury.

DISCUSSION

There are several reason why EEG abnormalities should now appear in patients with Parkinson's syndrome in contrast to the EEG abnormality noted in 1938 by Schwab and Cobb. The mean age of patients is now older as Schwab *et al.* (1956) have discussed. The average age of our present Parkinson population has increased to 65 from the 1938 value of 45. Several studies of the EEG in normals in this age group reveal 90 per cent normal records and it is not until the next decade and one-half that there is a slow rise in abnormality due to age itself.

With our special Clinic now in its tenth year, we have better opportunities to obtain serial chronological observations. There is nothing to suggest a change in the syndrome itself.

This condition, as has been summarized by Greenfield (1955) is correlated with some cell loss in the nuclei of the globus pallidus, considerable loss of pigment as well as nerve cells in the substantia nigra, and as far down as the locus caeruleus.

In patients who have had severe encephalitis prior to their Parkinson's disease and died rather early in life, the cerebral cortex is usually involved pathologically. Of course, when cerebrovascular disease develops in patients reaching the senium who also have Parkinson's disease involvement of the cortex and other cerebral structures is evident. If we only found these EEG abnormalities in the elderly Parkinson patient with obvious concomitant cerebrovascular disease we would have no problem in explaining them.

There is no correlation, however, with the age of the patient nor with the duration of the syndrome. This may be thought to be in keeping with the pleoform nature of the syndrome, which may appear over a wide period of years, may advance haltingly or steadily, and which may stabilize and cease to change at any point. It is, however, a very unfavorable sign when EEG abnormalities make themselves clearly apparent. For instance, the slow wave activity noted in the cases cited was found at a time when the patients were obviously much more handicapped than they had been.

The slow wave activity is correlated with the akinetic phenomenon which form such a devastating part of this syndrome. As Schwab *et al.* (1959) have pointed out, akinesia is conceived to encompass paucity and weakness of motion in general, both in simple movement and in complex patterns, such as those of walking, speaking, and swallowing. It does not embrace tremor or rigidity per se, although these are usually present to greater or lesser degree.

The severe forms of this akinesia are associated with sleepiness and yawning most of the day, lack of alertness and interest, and an exquisite sensitivity to sedative drugs. This suggests that the reticular activating system is involved in the pathology of this form of Parkinson's disease and that the slow waves in the EEG that are present reflect this involvement. This would agree with the slight but definite response that some of these pa-

tients show when large amounts of analeptics such as amphetamine and Metrazol are given to them as therapy.

The existence of EEG changes and of this akinesia is a prognostic sign of grave significance, indicating that the patient will not benefit greatly by neurolytic surgery, that such surgery is hazardous, and that he probably will prove to tolerate the usual medications with toxic reactions, especially confusion and dizziness. Thus, EEG normality is a helpful index in contemplating surgical intervention. We feel that in the presence of definite slow wave activity operation may be contraindicated. Very careful reevaluation of the patient is in order and air encephalogram, psychomotor tests, and measurements of the amount of akinesia present are indicated here.

The preliminary observations from depth recording in connection with Parkinson syndrome surgery on the globus pallidus and related structures have appeared unfruitful, as they have disclosed nothing that could be distinguished as a source of either tremor or rigidity. The post-operative records, in contrast, demonstrate clearly a focus of abnormality near the operated site, which is usually permanent. It would seem not surprising that a zone of permanent damage in subcortical structures tends to produce such a phenomenon. Bravo and Cooper (1956) have reported 160 records of 85 patients, noting no post-operative defect in 15 per cent, mild defects in 51 per cent, transitory defects in 18 per cent, and 9 cases with permanent defect due to operative complications, hemiplegias, etc. They have noted a decrease in mean alpha frequency, localized slow wave activity, and increased voltage on the operated side. Our results are quite compatible. It naturally follows that the EEG later will be of less clinical value in determining the advisability of re-operating on the contralateral side in such patients.

SUMMARY

1. The EEG is abnormal in 39 of 75 patients with Parkinson's syndrome. Of these 16 were mildly abnormal, 14 moderately, and 6 markedly so.

2. The abnormality is usually a random diffuse slow activity in the theta and delta range, most often restricted to the posterior portion of the head, occasionally dominant on one side or less commonly restricted to one side.

3. There is no obvious correlation with the clinical diagnoses of post-encephalitic arteriosclerotic, or idiopathic types of this condition. We have found this clinical sub-classification of very limited usefulness. Abnormalities are not related to the age of the patient nor to the duration of his disease.

4. EEG abnormalities are most closely related to the existence of those Parkinson's syndrome phenomena entitled "akinetic", and their appearance is an unfavorable sign for basal ganglion neurolytic surgery, as well as for improvement by the commonly used medications.

5. No consistent abnormalities have been seen by operative depth recording. A permanent focal slow wave focus is usually produced by basal ganglion destructive operations.

RÉSUMÉ

1. Trente-neuf sur 75 cas de syndrome Parkinsonien présentaient des EEG anormaux. L'EEG fut modifié de façon légère chez 6 cas, de façon modéré chez 14 cas, et de façon marquée chez 16 cas.

2. L'anomalie se voit souvent sous forme d'une activité lente diffuse sporadique pour les ondes théta et delta, limitée le plus souvent à la partie postérieure de la tête, parfois prédominante d'un seul côté, ou, plus rarement, localisée d'un seul côté.

3. Il ne semble pas y avoir de corrélation évidente entre les diagnostics cliniques des formes post-encéphalitiques, artério-sclérotiques ou idiopathiques de cette maladie. Nous n'avons trouvé qu'une utilité bien limitée à cette sous-classification clinique. Les anomalies n'ont pas de rapport avec l'âge du malade ou la durée de sa maladie.

4. Les anomalies EEG sont reliées le plus souvent à l'existence de ces syndromes Parkinsoniens dits « akinétiques », et leur apparition est un signe de mauvaise augure pour la chirurgie neurolytique des noyaux gris de la base, ainsi que pour l'amélioration par les médicaments d'usage commun.

5. Les enregistrements profonds opératoires n'ont pas démontré d'anomalies constantes. Les opérations lytiques des noyaux gris de la base donnent généralement lieu à un foyer permanent d'ondes lentes localisées.

ZUSAMMENFASSUNG

1. Ein abnormes Elektroenzephalogram wurde gefunden bei 39 von 75 Patienten mit Parkinson-Syndrom. Unter diesen zeigten 6 EEG nur geringfügige pathologische Veränderungen, 14 mässige Störungen und 16 ausgeprägte Abnormalitäten.

2. Die abnormen Veränderungen bestanden im allgemeinen aus unregelmässig diffus verteilten langsamen Aktivitäten im Theta- und Delta-Band, welche häufig auf die Hinterhauptregionen beschränkt waren. Gelegentlich dominierten diese Veränderungen auf einer Seite und in einigen wenigen Fällen waren sie auf eine Seite beschränkt.

3. Es bestand keine augenfällige Korrelation zwischen EEG und der klinischen Diagnose eines postenzephalitischen, arteriosklerotischen oder idiopathischen Parkinsonsyndroms. Die Autoren fanden, dass diese klinische Unterteilung nur von beschränkter Nützlichkeit ist. Abnorme Veränderungen standen weder in Beziehung zum Alter des Patienten noch zur Dauer seiner Krankheit.

4. Die abnormen EEG-Veränderungen zeigten die signifikanteste Beziehung zum "akinetischen" Symptomenkomplex des Parkinsonismus. Das Auftreten dieser Veränderungen muss als ein ungünstiges Indikationszeichen betrachtet werden, wenn eine neurochirurgische Behandlung des Parkinsonsyndroms durch einen Eingriff im Gebiet der Basalganglien in Erwägung gezogen wird. Ebenso ist die Prognose für eine Besserung mit medikamentöser Therapie in diesen Fällen eher eine schlechte.

5. Charakteristischen Veränderungen wurden keine gefunden, wenn tiefe Ableitungen während operativen Prozeduren ausgeführt wurden. Ein permanenter Herd langsamer Wellen ist im allgemeinen eine Folgeerscheinung, welche auf einen chirurgischen Eingriff im Gebiet der Basalganglien erfolgt.

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ANNOUNCEMENT

ADVANCED COURSE IN ELECTROENCEPHALOGRAPHY

At the 4th International EEG Congress in Brussels the General Assembly voted in favour of organising an advanced course in electroencephalography to be held at Marseille just before the 5th International Congress.

Provisional plans for this have now been drawn up by Dr. O. Magnus and Dr. W. Storm van Leeuwen in the form of a summer school in the week before the Congress. Further announcements will be made from time to time in this journal and all communications should be addressed to:

Dr. O. Magnus
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The Netherlands

MONORHYTHMIC FRONTAL DELTA ACTIVITY IN THE HUMAN ELECTROENCEPHALOGRAM: A STUDY OF 100 CASES [1]

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(Received for publication: October 30, 1958)

INTRODUCTION

Within the group of brain rhythms generally referred to as "rythmes à distance", the regular delta activity frequently seen in frontal regions of the EEG has been reported in a variety of physiological and pathological states. Several hypotheses have been formulated to explain its origin (for a summary, see Maleci 1952). This work was begun to study the distribution of this abnormality in various pathological states as a first objective and, if possible, to clarify some of the obscurities involved in its production.

METHOD

The EEG data cards of the Department of Applied Electrophysiology, The National Hospital, Queen Square, were searched through and when the report on the card indicated the possibility of "monorhythmic frontal delta" activity (MFD) the record itself was examined. Only those containing true MFD were kept, these three words expressing the necessary and sufficient conditions for the record to be included in our study (see fig. 1).

1. The frontal activity had to be regular. The waveform and amplitude were not determining factors. The occasional association of spikes with the slow waves or the occurrence of spike and wave complexes in the record did not exclude it from our group if episodes could be found of frontal delta rhythm without spikes.

2. The rhythm had to be frontal, i.e. seen in the first two channels of AP lines of electrodes with the National Hospital electrode placement, nearly identical to the 10-20 system (fig. 1). This did not exclude rhythms spreading to posterior regions if these were of greater amplitude anteriorly, or seen sometimes isolated in frontal regions.

3. It had to be within the delta range of frequencies.[3]

The records and hospital notes of the patients thus selected were re-examined and the data obtained registered on punch-cards according to a pre-arranged code. At the same time a short summary of the clinical history and the results of radiological examinations or surgical interventions were noted on the cards. Patients whose diagnoses had not been definitely established were discarded as unhelpful to the present purpose.

Since it is generally assumed that the rhythmic disturbance under study originates in deep central structures of the brain (see "Discussion" for references), evidence of "brain stem involvment" was constantly sought. The brain stem was considered as "involved" when:

1. Radiological, surgical or post-mortem evidence showed direct invasion of the brain stem by the pathological process.

2. Clinical neurological examination showed evidence of brain stem involvement either directly, or indirectly through herniation of one or both temporal lobes through the tentorium cerebelli and resulting compression of the brain stem. Clinical signs considered indicative of the latter condition were those list-

[1] Parts of this paper were presented at the London meeting of the EEG Society in January, 1958.

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[3] This regular rhythmic activity of rather constant frequency within the same record was called monorhythmic in line with a suggestion of Faure, Drooglever-Fortuyn, Gastaut, Larramendi, Martin, Passouant, Remond, Teteca and Walter (1951).

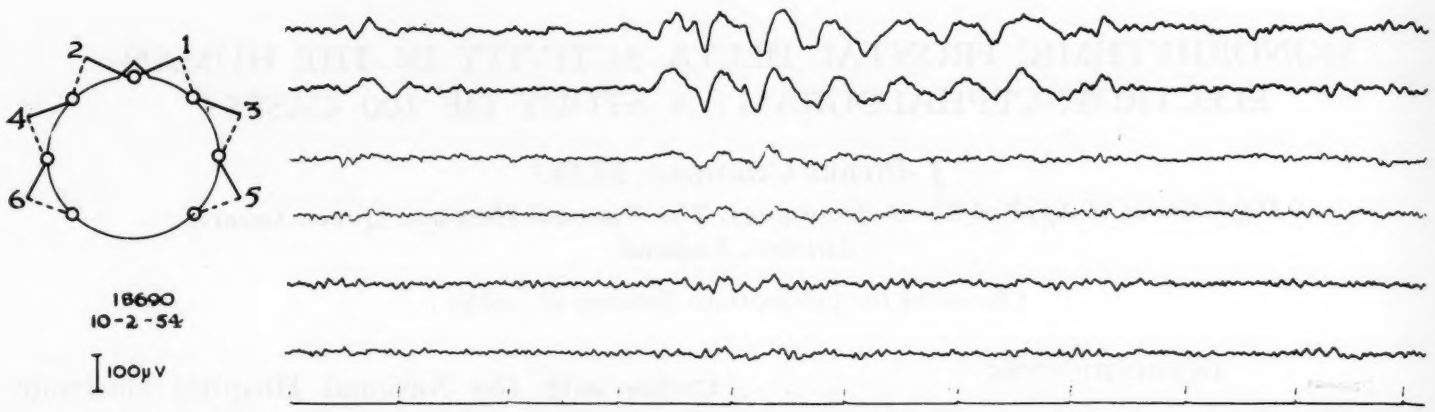

Fig. 1

Example of the monorhythmic frontal delta activity (MFD) as discussed in the text. This is a sample from the EEG record of a 51 year old woman taken three weeks after a bilateral prefrontal leucotomy (EEG number: 18690). A preoperative record did not show this abnormality.

ed by Jefferson (1938) and Johnson and Yates (1955).

As will be seen later, in the great majority of cases where the brain stem appeared to be involved, this was due in all probability to tentorial herniation of temporal lobe structures.

RESULTS

A. *Pathology.*

With the above criteria in mind, 100 patients with monorhythmic frontal delta activity in their EEG records were found in a total number of 8,200 records searched (EEG No. 17,800 to 26,000); the final diagnoses of these patients were distributed as follows:

Tumours (including abcess)	43
Epilepsy (idiopathic or symptomatic of unknown etiology)	25
Psychiatric disturbances	11
"Degenerative" diseases	8
"Vascular" diseases	7
Infection (meningitis)	3
Head injury	2
Aqueduct stenosis	1
Total:	100

A further breakdown of the above classification, with the most probable cause of the MFD in mind, gives the distribution of pathology listed in table I. Certain vascular conditions are included under "Space Occupying Lesions" under the assumption that their space occupying quality, or that of the accompanying oedema, was the direct cause of the MFD rather than the vascular pathology itself.

At first sight, there appear to be only 7 cases in which the brain stem or deep mid-line structures are directly involved in the known pathological process, and only 9 in which the posterior fossa is the site of the lesion. This is rather surprising as we expected to see the distribution more heavily weighed in favour of brain stem, mid-line, or posterior fossa lesions. In order to make sure that no lesion in these sites had been missed through the selection method used, a systematic search for MFD was made in the known cases of posterior fossa or deep mid-line lesions with EEG records. No further cases were found for the period already investigated, but 4 MFD records were selected from the preceding period and on the same criteria. Table II shows the total number of posterior fossa and brain stem lesions investigated from 1949 to 1956 inclusive, with the corresponding number showing MFD. Therefore, out of 100 cases of MFD, 12 had lesions directly involving the brain stem, deep mid-line structures or the posterior fossa, and out of a total of 137 such lesions, 15 (or approximately 11 per cent) showed MFD.

However, of the 40 supratentorial space occupying lesions (table I), 22 showed some clinical or radiological sign which could be interpreted as brain stem involvement, most probably through temporal herniation and re-

TABLE I

Distribution of pathology in 100 patients with monorhythmic frontal delta activity (MFD) in their EEG records.

	No. with MFD	No. investigated during same period
A. *Space Occupying Lesions: (49)*		
(*a*) Supra-tentorial (40)		
1. Gliomas:	25	153
Frontal	13	47
Temporal	5	39
Parietal	3	27
Corpus callosum	2	7
Fronto-temporal	1	7
Thalamus	1	4
2. Meningiomas:	3	71
Frontal (parasagittal)	1	
Convexity (parietal)	1	
Pterion	1	
3. Pineal tumour	1	
4. Supra-sellar epit. tumour	1	
5. Metastasis (unlocalized)	3	29
6. Vascular:	6	
Subdural haemetomas	2	10
Carotid aneurysm	1	
Cerebral haemorrhage	1	
Cerebral thrombosis	1	
Sagittal sinus thrombosis	1	
7. Abcess (Fronto-parietal)	1	
(*b*) Infra-tentorial (9)		
1. Gliomas (brain stem)	4	19
2. Cerebellar:	5	22
Haemangioblastoma	3	
Metastasis	1	
Benign cyst	1	
B. *Epilepsy* (idiopathic or symptomatic of unknown etiology)	24	
C. *Prefrontal leucotomy*	8	
D. *"Degenerative diseases"*:	8	
Cortical atrophy	4	
Disseminated sclerosis (encephalitic type)	1	
Sydenham's chorea	1	
Cerebral lipoidosis	1	
Unspecified	1	
E. *Neurosis (one with ECT)*	3	
F. *Aqueduct stenosis*	1	
G. *Vascular disease (arteriosclerosis)*	1	
H. *Infection (meningitis)*	3	
I. *Head injury*	2	
J. *Metrazol activation*	1	
Total:	100	

TABLE II

	No. of Cases Investigated	No. of Cases with MFD
Neoplasms — brain stem	19	4
" cerebellar	49	7
" colloid cysts (IIIrd. Vent.)	12	0
" neurofibromas (VIIIth nerve)	39	1
" pinealoma	2	1
Aqueduct stenosis	16	2
Total:	137	15

Total number of posterior fossa and brain stem lesions investigated in the EEG department, National Hospital, Queen Square, from 1949 to 1956 inclusive, with the corresponding number showing monorhythmic frontal delta activity in their EEG records.

sulting brain stem compression. Furthermore the absence of such signs cannot be construed as complete freedom of the brain stem from the effects of temporal herniation since at least 11 other cases showed some signs or raised intracranial pressure, and as stated by Johnson and Yates (1956): "Sometimes..., the rise of pressure is slowly progressive... and the most striking atrophies, displacements, and ventricular herniations are produced at tentorial level with little or no clinical change."

B. *Space Occupying Lesions.*

This group includes 6 cerebrovascular accidents since it is assumed that these produce MFD because of their space occupying quality rather than through the specific vascular pathology. It also includes the 3 tumours obtained from a search of the known cases of brain stem and posterior fossa lesions, giving a total of 52 space occupying lesions. The average age of this group was approximately 48 years, the youngest patient being 17 and the oldest 67 years of age. Eighteen of these patients had one or more "fits" noted in their

Certain vascular conditions are included in the space occupying lesions under the assumption that their space occupying quality is responsible for the MFD rather than the vascular pathology itself. The first column shows the number of patients with MFD in their EEG records, while the second shows the corresponding number of patients investigated in the EEG department, National Hospital, Queen Square, during the same period, where this figure was available.

clinical history. These ranged from simple loss of consciousness to grand mal attacks preceded in some by a Jacksonian march.

(*a*) *Characteristics of the MFD.*

(1) *Frequency.*

No correlations could be established between the frequency of the MFD and the nature or site of the lesion, at least within our arbitrary limits of "faster than 2 c/sec." and "2 c/sec. and under"; 13 records showed a frequency greater than 2 c/sec. and 39 one of 2 c/sec. and under and in general the faster frequencies belonged to the younger age group. The two were rather evenly distributed within the different groups of space occupying lesions. The frequency seldom varied much from this mean of 2 c/sec., being rarely greater than 3 c/sec. and never going much below 2 c/sec. The same record was sometimes observed to contain MFD at varying frequencies extending on each side of our arbitrary limit of 2 c/sec. In a few cases some frontal theta rhythm at 4 or 5 c/sec. was seen in the resting record, gradually slowing down during overbreathing to 2 or 3 c/sec., thus coming within our terms of reference. This same observation was reported by Daly *et al.* (1953).

(2) *Waveform.*

The commonest waveform was saw-tooth, with a rapid rising phase and a more gradual descending one. Frequently interspersed with it and second to it in frequency of occurrence, was a smoother type with more equal rising and falling phases somewhat similar in morphology to what were once described as psychomotor waves. All transitions between these two forms could usually be seen and neither appeared to be associated with any specific localization or variety of brain tumour.

Only one record of the tumour group showed a spike occasionally linked with the waves of the MFD. This was from a case of a grade II astrocytoma of the right frontal lobe in a 44 year old woman with a 7 year history of "fainting fits" sometimes followed by convulsions, incontinence and tongue biting. The MFD episodes were left sided and were reported as probably due to secondary bilateral synchrony (Penfield and Jasper 1954), the lesion preventing their appearance on the right side.

(3) *Spatial distribution.*

In 14 cases the MFD was strictly bilateral and symmetrical.

In 15 it was of greater amplitude or seen more frequently on one side. Of these asymmetrical records: 12 showed more MFD on the side of the lesion; 2 more on the opposite side, and in 1 case there was more MFD on the side to which a glioma of the pons and midbrain extended into the temporal lobe.

In 23 cases the rhythmic abnormality was strictly unilateral: 20 on the side of the lesion, 2 on the opposite side, and one was unilateral with a mid-line cerebellar cyst.

These facts confirm the generally accepted finding of the strong correlation between unilateral or asymmetrical MFD and the laterality of the lesion. The cases which deviate from this rule (3 frontal gliomas and 1 large carotid aneurysm) can probably be explained by the associated tissue destruction which prevents the rhythmic delta from coming through on that side. All 4 exceptions were frontal lesions where the destruction involved was quite extensive, and this could be surmised from the large amount of polyrhythmic or irregular delta activity localized to this region. An interesting point is that this lateralization of the MFD to the side of the lesion holds also for cerebellar tumours in 5 of our 8 cases; 2 others had a strictly bilateral spread and in one the MFD was unilateral with a mid-line cerebellar cyst. These findings are in direct contradiction to those reported by Bagchi *et al.* in 1952.

In most of the unilateral MFD group, but not in the bilateral, a focus could be surmised though only rarely accurately located. Furthermore it was often seen to shift position at different times throughout the record or in successive records. The most frequent position of the focus was far anteriorly and low down which is in close agreement with the findings of Fischgold *et al.* (1950), using special monopolar derivations to determine the site of maximal amplitude of the MFD in cases of meningiomas.

(4) *Temporal distribution.*

The MFD with space occupying lesions is a rather labile phenomenon appearing or disappearing from successive records, without any apparent change in the clinico-pathological state of the patient. From the few cases in which we were fortunate enough to obtain several recordings over a period of time before surgery or autopsy, it was impossible to establish any trend of increase or decrease of MFD with progression of the tumour process.

However, when the patient's condition improved following surgery, or with the passage of time after a cerebro-vascular accident, the MFD would decrease in frequency of occurrence, or disappear completely from the record, to be brought out again in overbreathing . . . and then not at all.

(5) *Reactivity.*

In the 52 cases of space occupying lesions the MFD was increased in none, decreased in 8, and not affected in 19 by eye opening. In 25 cases the episodes were too few to permit this assessment.

In the same group, the MFD was reported as increased in 25, decreased in 1, and not affected in 6 by overbreathing. In 20 cases the effect of this procedure could not be determined, usually due to the incapability of the patient to understand what was required of him.

(*b*) *MFD and mental disturbances.*

Twenty-eight of the 52 patients with space occupying lesions showed some type of mental disturbance (as distinct from simple drowsiness or disorders of consciousness and from personality disorders). These were variously described as "deterioration of memory and behaviour", "mental slowness", "difficulty in concentration", "progressive vagueness", "confusion", "progressive organic dementia", "disorientation in time and space", etc.

The following points seem to argue for a more than chance relationship between monorhythmic frontal delta activity and mental disturbances:

(1) The high incidence of mental disturbances in the remaining groups reported here, this condition being present in 15 out of 43 patients excluding the post-leucotomy cases.

(2) The presence of MFD in patients with cortical atrophy where the only, or main symptom, was progressive dementia.

(3) The MFD which follows leucotomy for a short period of time and which may coincide with the tempory "dullness' or "disorientation in space and time" known to occur following this intervention (Freeman and Watts 1950).

It might be interesting to know whether there is any correlation between frequency of bursts of MFD and presence or degree of mental disturbance.

(*c*) *MFD and site of space occupying lesion.*

No clear cut correlations between the presence of MFD in the EEG records and the sites of the lesions causing it are apparent at least within the limited accuracy possible in this study. As can be seen from table I, MFD is found with approximately 1 in 4 tumours of the thalamus, corpus callosum, frontal lobes, and cerebellum; with 1 in 5 brain stem gliomas and approximately 1 in 8 temporal and parietal gliomas. These differences may not be significant in view of the small numbers involved in each group and the limited accuracy possible in defining supratentorial tumours without full surgical or autopsy control. The possibility of a tumour reaching a considerable size in a "silent area" such as a frontal lobe before medical counsel is sought might account for greater association of MFD with one more than another. However, the rate of growth of the tumour process may be a determining factor since meningiomas produce MFD in the proportion of 1 in 24 as opposed to 1 in 6 for all gliomas and 1 in 5 for subdural haematomas.

C. *Epilepsy.*

This group includes 24 patients whose only clinical diagnosis was that of epilepsy, occasionally described as "symptomatic", " . . . of late onset", or "post-traumatic". In 22 of the 24 cases the epilepsy was thought to be of the symptomatic variety by the electroencephalographer; in 10 there was a suggestion of deep

frontal or mesial frontal lesion with secondary bilateral synchrony; in 7 the record was thought to be indicative of a lesion of the deep mid-line or central structures, and 5 were reported as probable symptomatic epilepsy without localizing features. These EEG suggestions are neither confirmed nor denied by the clinical diagnosis, based on the history and examination of the patient, skull radiographies and, in only a very few cases, on air studies. In all evidence, it follows from the method of classification adopted here that all epileptics, in whom the causal lesion was diagnosed with some degree of certainty, are automatically excluded from this group, and we have seen that 18 patients with space occupying lesions showed a history of fits. In the present group the nature and cause of the epilepsy still remains obscure and such lesions as a meningocerebral cicatrix, a localized zone of cortical atrophy or a small hemangioma are not ruled out by the investigations carried out.

The average age of this group was considerably lower than that of the space occupying lesion group: the youngest patient being 6½, the oldest 74, and the average age 28; 19 were below 40 years of age and only 5 above. The length of time between the first epileptic fit and the first EEG varied from about 1 to 26 years, the average being 8 years. In 8 cases the epilepsy was attributed to brain injury, through difficult birth (2), head trauma (3), or brain surgery (3). Eight patients showed mental retardation or behaviour disturbance.

The types of attack fell into the following categories:

Mixture of minor and major attacks without aura (i.e. with initial loss of consciousness)	8
Major attacks without localizing signs	8
Loss of consciousness sometimes followed by localized "twitching"	6
Doubtful temporal lobe attacks	1
Myoclonic jerks of head and arms	1

From the EEG point of view: 12 records showed some type of spike and wave phenomena, variously described as "ragged", "asymmetrical" or more frequently as "rhythmic slow waves with occasional spikes", thus accentuating the fact that the slow wave was the important phenomenon and the spike quite accessory. None of these spike and wave were of the classical petit mal type and between these episodes there occurred bursts of rhythmic delta which answered the criteria of our MFD series. Twelve records did not have a true spike component but in a few the slow rhythmic waves were sometimes described as "notched" or with "phantom spikes".

The presence of spike and wave complexes correlates with the younger age group, the average age with spike and wave being 17 years, and the average without spike and wave 41 years. It also agrees with the presence of minor attacks in the history of the patient, all 8 patients with such attacks showing complexes in their records.

With regard to the monorhythmic frontal delta activity, some episodes could usually be found in each record, which, if isolated from the context, could have been seen in a patient with a tumour, and all varieties and transitional forms between these and more or less well formed spike and wave complexes could be observed in the same record. Two cases, not included in this group, are interesting in this respect, both showing the gradual development of spike and wave complexes from a background of MFD over a period of days or weeks and through several recordings. One was diagnosed as "disseminated sclerosis - encephalitic type", the other as encephalitis of obscure origin.

The distribution and morphology of MFD were similar to those found with space occupying lesions. A possible difference between the two may be one of frequency; 18 were over 2 c/sec. and only 6 were 2 c/sec. or under. Whether this is an indication of a different physio-pathological mechanism or just a reflection of the difference in the age groups is an open question, but from the trend observed in the tumour group the latter seems the more probable.

The effects of eye opening and overbreathing were similar in the two groups;

5 cases showed blocking of the MFD with startle stimuli, usually of an auditory nature (clap, whistle, etc.).

D. *Prefrontal Leucotomy.*

There were 8 cases where MFD followed upon bilateral prefrontal leucotomy. In 7 a preoperative record showed normal electrical activity or at least no abnormality of the type we are concerned with. The postoperative records (2 to 3 weeks) contained bilaterally synchronous monorhythmic frontal delta as the sole important new abnormality. This MFD had the same general distribution, waveform and characteristics as that seen with space occupying lesions. In 2 cases a later record (2 months postoperatively) had returned to the preoperative state and the MFD had disappeared.

E. *Cortical Atrophy.*

In 4 cases with MFD the final diagnosis was that of cortical atrophy, based on a clinical history of progressive dementia and on radiological air studies. In one case this diagnosis was confirmed at autopsy. The abnormality observed in the EEG records was similar to that of the other categories discussed previously and was sufficient for the electroencephalographer to suggest the possibility of a deep mid-line lesion in each case.

DISCUSSION

The present study shows the occurrence of monorhythmic frontal delta rhythm to be rather unspecific: it may also occur in a wide variety of physiological or experimental conditions (see Maleci 1952). This causal variety decreases its diagnostic value as an isolated phenomenon and unless the history and clinical examination of the patient, or the associated EEG abnormalities, give some clue to its significance, it would appear to be unsafe (and probably misleading to the clinical neurologist) to report its presence as indicative of a brain stem lesion or dysfunction. On a purely statistical basis, and taking into account the frequency of occurrence of tumour types seen at the National Hospital, we would agree with Van der Drift's (1957) conclusion that MFD is most likely to indicate a deep mesio-frontal space occupying lesion, and if this is so, the chances are that it will be a glioma. However, this is not a very useful generalization if we consider the wide variety of pathological states and tumour localizations associated with this rhythm, and until more is known of its origin and pathophysiological mechanism, its usefulness as a diagnostic sign is likely to remain low.

In the past, several clinical EEG correlation studies have been published, showing the association of this rhythm with a large variety of tumours and tumour sites (Lennox and Brody 1946; Laufer 1947; Bickford and Baldes 1947; Gastaut and Tamalet 1949; Fischgold, Dreyfus-Brissac and Scarpalezos 1950; Lairy-Bounes and Dreyfuss-Brissac 1950; Martin and Martin 1950; Faure *et al.* 1951; Gros, Passouant and Billet 1951; Jasper and Van Buren 1953; Gastaut 1954; Inghirami and Arfel-Capdevielle 1954; Passouant, Cadilhac and Vlahovitch 1955; Van der Drift 1957 etc.). All agree on the necessity of a deep subcortical pacemaker. The critical area is usually placed in the upper midbrain or basal diencephalon, and this conclusion is often based on necropsy studies where the sites of maximal and most frequent destruction by the diencephalic or brain stem lesion were looked for and incriminated in the production of MFD. It followed logically that space occupying lesions in outlying regions of the cerebrum must act through a distortion or compression of these sites. One possible objection to this method is that the characteristics of this abnormality and its frequent association with epilepsy make it more likely to be the result of an irritative or excitatory process rather than that of a destructive one. Therefore it does not necessarily follow that a tumour in the midbrain or basal diencephalon will localize the area responsible for the MFD. As in the case of outlying tumours, this one may act through irritation or compression of other structures.

On the other hand, neurophysiological studies in animals would place the pacemaker responsible for the regular frontal delta activ-

ity in that region of the thalamus which includes the dorso-medial nucleus and surrounding intralaminar nuclei. For example, Jasper and his colleagues have amply shown this thalamic region to be capable of sustaining a slow wave rhythmic discharge in the frontal lobes at or about a frequency of 3 c/sec. which they compare to that seen in petit mal epilepsy (Jasper, Droogleever-Fortuyn 1946; Jasper, Hunter and Knighton 1948; Hunter and Jasper 1949). These slow waves may be free of or accompanied by spikes, according to the localization of the stimulating electrode. Of particular interest in this respect is a recent paper by Ralston and Ajmone-Marsan (1956), where these authors show that the injection of small amounts of penicillin into various areas of the thalamus of unanesthetized cats or of animals under barbiturate anesthesia is routinely followed by slowing of the 8 - 12 spindles to 3½ - 5 c/sec. and by their synchronization over widespread areas of the cortex. They show that the distribution of this slowing depends on the localization of the thalamic injection and that injections in mesial thalamus produce spindle alteration confined to or beginning in the anterior regions of the hemispheres. Each side may be activated separately or synchronously depending on the distance of the injection from the mid-line and the spread of the penicillin with time. Through control experiments they then proceed to show that the slow cortical activity is due to an irritation of the thalamic structure involved rather than to its destruction, and discuss their findings in relation to pathological theta or delta rhythms seen in the human EEG. Whether or not these human pathological rhythms are slowed sleep-spindles is not our concern here, but their work is important to us in that it shows the probable site of origin of MFD in the mesial region of the thalamus. This would agree with the conclusions of Van der Drift's (1957) clinical study mentioned above. Based on a large number of necropsy findings, this author states that the dorso-medial nucleus of the thalamus must be intact for the MFD to appear in the EEG record.

Therefore if we assume that the monorhythmic frontal delta activity originates in the mesial thalamus when this structure reaches a sufficient degree of excitation, and that it may be thus excited by an abnormal bombardment through one of several possible afferent pathways, it becomes possible to understand the probable mechanism involved in some of the pathological groups of our study.

One group concerns the MFD seen following bilateral prefrontal leucotomy. We have 8 such cases in our series. Records were obtained pre-operatively and contained no abnormality of the type discussed here. On an average of 2 weeks post-operatively, a second record showed bilaterally synchronous MFD which had disappeared after 2 months when further records were obtained in 2 cases. The anatomical studies of Freeman and Watts (1947), Meyer (1949), McLardy (1950) and others have shown one of the principal areas of generation following this intervention to be the dorso-medial nucleus of the thalamus. It could be argued that following surgery and during the period of degeneration and gliosis, a ''state of excitation'' is entertained in this thalamic structure sufficient to produce MFD through the remaining intact fibers to the frontal lobes.

In the epileptic group it was noted in our results that 22 out of the 24 cases were reported as probable symptomatic epilepsy and that in nearly half of these the suggestion was of a frontal origin for the abnormal discharge. In his original and later descriptions of ''secondary bilateral synchrony'', Jasper suggests the medial surface of the frontal lobe as a site most favourable for the production of this rhythm, and in fact in all cases quoted the lesion sits either in the parasagittal cortex of the frontal lobes or on its orbital surface (Penfield and Jasper 1946; Tukel and Jasper 1952; Penfield and Jasper 1954). Case L. Fr. in the latter reference in particular shows a frontal bilaterally synchronous rhythm at 2.5 to 3 c/sec., without spikes very similar to the rhythm with which we are concerned here. Because of the to and fro connections between the frontal cor-

tex and the mesial and anterior thalamus, it may be that the rhythmic frontal delta observed in our epileptic cases during the intervals between spike and wave complexes is also due to a state of excitation of this portion of the thalamus, and that the generalized spike and wave phenomenon only appears when this state of excitation exceeds a certain threshold and "overflows" into other thalamic or centrencephalic structures, in line with an hypothesis formulated by Hunter (1950). The necessity for a stronger stimulus and a spread of the excitation before the appearance of the spike component in the spike and wave complexes is also discussed by Ralston and Ajmone-Marsan (1956) in their paper discussed at length above. In matter of fact the MFD observed in these epileptics was very often strikingly similar to that seen in brain tumours. It would gradually evolve and spread to other regions at the same time as the spike component appeared just as if other subcortical structures were gradually being recruited and brought into play.

Case No. 24466 is interesting in this respect. This 49 year old man had a bilateral prefrontal leucotomy in 1948. Following this surgical intervention he developed occasional epileptic fits characterized by sudden loss of consciousness followed by generalized convulsions. An EEG taken on 24-1-56 (8 years post leucotomy) showed moderate voltage rhythmic 2 to 3 c/sec. bilaterally synchronous slow waves in the resting record sometimes better seen on the left. There had been no EEG record taken at the time of the leucotomy so no comparison can be made between the present MFD and that which may have existed 8 years ago, but it is conceivable that the leucotomy scar, having become epileptogenic, fired the same electrophysiological mechanism as the immediate post-operative irritative state. The rhythm in this case is considered as a manifestation of the epileptic activity of the frontal lobe and may serve as a clue in linking the MFD following prefrontal leucotomy and that associated with epilepsy of frontal lobe origin, arguing for a common physiological mechanism in the two groups.

The third group concerns the MFD seen in a few cases of meningitis and with diencephalic or basal tumours. This can be linked to the report of Passouant *et al.* (1955) following their study of cases of meningoencephalitis, optochiasmatic arachnoiditis and basal tumours, in which they conclude that impairment of the circulation to the anterior and lateral hypothalami area is the essential factor in the production of MFD. These observations can probably be integrated in our present hypothesis of a mesial thalamic pacemaker for MFD. The anatomical studies of LeGros Clark (1938, 1948) have shown the existence of a fiber system, originating in the whole antero-posterior extent of the hypothalamus, running close to the ependymal lining of the wall of the third ventricle and terminating in the medially placed nuclei of the thalamus especially the dorso-medial nucleus. This is confirmed by the physiological studies of Murphy and Gellhorn (1945) in the cat, where application of strychnine in the anterior or posterior hypothalamus produced a discharge in the dorso-medial nucleus of the thalamus as the main preferential pathway. Therefore it may be that in Passouant's, as well as in our own observations, the dorso-medial nucleus, being submitted to a barrage of impulses from the hypothalamus, reached a sufficient excitatory state to produce monorhythmic frontal delta activity.

In the larger group of space occupying lesions, it is probable that the MFD which accompanies certain tumour sites such as frontal gliomas or meningiomas could also be explained by impulses reaching the mesial thalamus along one of the pathways discussed above. But in most cases the origin of the abnormal bombardment is not immediately apparent. By carrying these speculative considerations further, it is suggested that the medial temporal lobe structures involved in temporal herniation through the tentorium cerebelli may, at times, be responsible for the frontal abnormality. Temporal herniation is a frequent accompaniment of space occupying lesions; it may proceed directly from mechanical displacement of the brain substance and/or through the agency of raised

intracranial pressure and it is usually greater or confined to the side of the lesion (Azambiya, Lindgren and Sjorgen 1956). The following evidence could be marshalled in support of such an hypothesis.

Anatomically there are several pathways linking the rhinencephalic structures of the temporal lobes and the mesial and anterior thalamus. Apart from the better known fornix fibers linking the hippocampus to the mammillary nuclei and hypothalamus bilaterally (Simpson 1952; Adey and Meyer 1952) and from there to the anterior thalamic nucleus through the mammillo-thalamic tract, there appear to be other fibers providing a direct path from the amygdaloid nucleus to the dorso-medial nucleus of the thalamus (Fox 1949) and a further important contingent of fornical fibers leaving this structure and entering the dorso-medial nucleus directly (Knighton, as quoted in Penfield and Jasper 1954, pp. 176 and 179).

Physiologically it has been shown that structures of the medial surface of the temporal lobe are capable of a widespread and varied influence on the electrical activity of cortical and subcortical structures in cats and monkeys (see Kaada 1951; Green and Shimamoto 1953; Morin and Green 1953; Naquet 1954; Gloor 1954; Walker, Andy and Faeth 1954). Some of these authors have stressed the low convulsive threshold of these structures, particularly that of the hippocampi and fimbria, and their great sensitivity to a mechanical type of stimulation such as introduction of electrodes or gentle stroking with cotton wool, procedures which were sufficient to produce prolonged after-discharges.

Kaada (1951) reporting on his experiments on stimulation of, and spread of after-discharge from rhinencephalic structures writes: "In 3 monkeys and 1 infant chimpanzee ... the sensory-motor and frontal polar areas were predominantly influenced ... The self sustained discharges elicited from the tip of the hippocampal gyrus and adjacent temporal polar region in monkeys and infant chimpanzee were usually fairly characteristic of a low frequency type (1.5 to 4 per sec.) although some higher frequencies e.g. 6-10/sec. were occasionally noted ... Long lasting discharges could be recorded from these regions with no significant change in the spontaneous activity of other neocortical fields ... A high incidence of slow wave (1.5 to 4 per sec.) after-discharges similar to those recorded in the present investigation on stimulation of the anterior end of the hippocampal gyrus and temporal pole has also been noted in human epileptics on stimulation of the same areas."

This tendency of the rhinencephalic structures to give rise to slow rhythmic discharges in the anterior portions of the cerebral hemisphere in the infant monkey was confirmed by Walker, Andy and Faeth (1954). They showed further that the dorso-medial and intralaminar nuclei of the thalamus can be selectively implicated in the after-discharge.

Therefore it would appear that at least under experimental conditions, the structures directly involved in temporal herniation are particularly sensitive to a mechanical type of stimulation and can give rise to slow wave discharges in the anterior portions of the cerebral hemispheres.

From a clinical electroencephalographic standpoint, in the tumour group of this study, temporal herniation through the tentorium cerebelli was probably the most frequent single common factor, either observed directly or surmised from the existing evidence. It was present in 11 of the 12 cases with autopsy control, usually confined to or greater on the side of the delta activity when this rhythm was asymmetrical or unilateral. Of the remaining 31 supra-tentorial space occupying lesions, 13 showed definite clinical signs or symptoms of brain stem involvement through temporal herniation and resulting brain stem compression (Jefferson 1938; Johnson and Yates 1956). A further 12 cases had signs of increased intracranial pressure such as papilloedema or erosion of the sella turcica and as stated by Johnson and Yates (1956): "Sometimes the rise of pressure is slowly progressive ... and the most striking atrophies, displacements and ventricular herniations are produced at tentorial level with little or no

clinical change.'' Of the 9 posterior fossa lesions which did not reach autopsy, all had raised intracranial pressure. Therefore it seems that in the majority of our space occupying lesions with MFD, there is some direct or indirect evidence of temporal herniation through the tentorium cerebelli.

The close correlation between MFD and raised intracranial pressure (presumably accompanied by temporal herniation) was also noted by Van der Drift (1957) in his large series of brain tumours. He came to the conclusion that all space occupying lesions showing MFD were accompanied by an increase in pressure. The only exceptions to this rule were frontal tumours where raised pressure did not appear to be a necessary condition for the preduction of this rhythm. This same correlation was also noted by Williams (1939), Bagchi *et al.* (1952) and Daly *et al.* (1953). In their study of EEG findings in subdural haematomas, Rodin, Bickford and Vien (1953) also stressed the close correlation between what they called ''dysrhythmia'' (our present MFD according to their description) and clinical or radiological signs of brain stem distortion. This distortion was probably due in most, if not all cases, to temporal herniation.

Therefore it may be that temporal herniation is a prime factor in the production of rhythmic frontal delta activity in some cases of brain tumours. As discussed previously, temporal lobe structures distorted by the herniation would fire the mesial thalamus which in turn would produce the MFD. At the present time this can only be considered as a plausible hypothesis. Further confirmatory evidence is needed before it can be accepted as fact.

SUMMARY

Within the group of brain rhythms, generally referred to as ''rythmes à distance'', the regular delta activity frequently seen in frontal regions of the EEG has been reported in a variety of physiological and pathological states. Several hypotheses have been formulated with regard to its origin. This work was begun to study its distribution in various pathological states as a first objective and, if possible, to clarify some of the obscurities involved in its production.

One hundred EEG records, containing this rhythm, were picked out from the index cards of the Department of Applied Electrophysiology, The National Hospital for Nervous Diseases, Queen Square, London. The electroencephalograms, clinical notes, radiological, surgical and post-mortem reports were examined and analyzed and the data obtained registered on punch cards according to a prearranged code.

The results obtained confirm the lack of specificity of this abnormality and deny it any value as an indicator of the direct involvement of the brain stem or posterior fossa by the pathological process.

From the data presented and the literature reviewed, it is suggested that the medio-dorsal area of the thalamus may be involved in the production of monorhythmic frontal delta activity, whenever this structure reaches a sufficient degree of excitation and that this degree of excitation may be the result of impulses reaching it along one of several possible afferent pathways. In some cases of brain tumours, it is suggested that the pathway interested may be that linking this area of the thalamus with the structures on the mesial surface of the temporal lobe involved in temporal herniation, the frequent accompaniment of space occupying lesions. On the other hand, the monorhythmic frontal delta activity frequently seen for a short period of time following prefrontal leucotomy is probably best explained by a state of excitation in the medio-dorsal nucleus of the thalamus produced by the degeneration and gliosis which have been shown to occur in that area following this intervention.

RÉSUMÉ

Ce rapport étudie la distribution de la pathologie nerveuse chez 100 malades dont l'électroencéphalogramme présente une activité delta monorythmique à localisation frontale (MFD).

Les résultats obtenus montrent que cette activité frontale monorythmique peut être le témoin d'une grande variété d'états pathologiques et par conséquent confirment la non-spécificité de ce phénomène électrocortical.

A partir de cette étude et nous basant sur les travaux déjà publiés sur ce sujet, nous proposons l'hypothèse suivante quant à l'origine de cette activité: le MFD se manifesterait dans l'électroencéphalogramme lorsque le noyau dorso-médian du thalamus atteint un certain niveau seuil d'excitation. Ce niveau d'excitation du noyau dorso-médian à son tour peut être le résultat d'influx excitateurs lui arrivant par l'une ou l'autre de plusieurs voies afférentes possibles. Les voies fronto-thalamiques sont probablement intéressées là où il s'agit de tumeurs frontales ou lorsque le MFD suit la leucotomie préfrontale. Les tumeurs ou infections de la base produiraient ce rythme delta frontal par l'intermédiaire des voies hypothalamo-thalamiques qui se terminent dans le noyau dorso-médian. Enfin, il est possible que certaines tumeurs cérébrales agissent par l'intermédiaire des voies afférentes au noyau dorso-médian dont l'origine se trouverait dans les structures rhinencéphaliques du lobe temporal. D'une part ces structures sont très souvent déformés par suite d'une herniation temporale dans la tente du cervelet et d'autre part on connait leur grande susceptibilité à toutes formes de stimulation mécanique.

ZUSAMMENFASSUNG

Es ist verschiedentlich mitgeteilt worden, dass unter den Hirnrhythmen, welche im allgemeinen als ''rhythmes à distance'' bezeichnet werden, die regelmässige Delta-Aktivität, welche häufig im EEG der Frontalregion registriert werden, in einer Gruppe von verschiedenen ''physiologischen'' und pathologischen Zuständen vorkommen kann. Verschiedene Hypothesen über den Ursprung dieses Rhythmus sind aufgestellt worden. Die vorliegende Arbeit wurde begonnen im Bestreben, zunächst die Verteilung dieses Rhythmus bei verschiedenen pathologischen Zuständen zu studieren, und wenn möglich gewisse Probleme seines Ursprungs klarzustellen.

Hundert EEG-Aufzeichnungen, in welchen dieser Rhythmus auftrat, wurden von Indexkarten der Abteilung für angewandte Elektrophysiologie des ''National Hospital for Nervous Diseases'', Queen Square, London, ausgewählt. Die Elektroenzephalogramme, klinische Aufzeichnungen, Roentgenberichte, Operationsberichte und Autopsiebefunde wurden geprüft, und die so gewonnenen Daten auf Grund eines im voraus ausgearbeiteten Kodifizierungssystem auf Lochkarten übertragen. Die so gewonnenen Resultate bestätigen das Fehlen jeglicher spezifischer Korrelation dieser Abnormalität und zeigen, dass dieser Befund nicht als diagnostisches Zeichen für das Vorliegen eines pathologischen Prozesses im Hirnstamm oder in der hinteren Schädelgrube betrachtet werden kann.

Sowohl diese Befunde als auch Mitteilungen in der Litteratur machen es wahrscheinlich, dass diese monorhythmische, frontale Deltaaktivität mit der mediodorsalen Region des Thalamus in Beziehung steht. Diese abnorme Aktivität im Stirnhirn tritt wahrscheinlich immer dann auf, wenn ein genügender Grad der Erregung in dieser thalamischen Struktur auftritt, wobei der Grad dieser Erregung die Folge von Einströmen von Impulsen sein könnte, welche den Thalamus über verschiedene, afferente Bahnen erreichen könnten. In gewissen Fällen von Hirngeschwülsten bestehen Anzeichen, dass eine wichtige solche Bahn diejenige sein könnte, welche diese Region des Thalamus mit denjenigen Strukturen der medialen Fläche des Schläfenlappens verbindet, welche üblicherweise in Fällen von temporaler Herniation, im Gefolge raumbeengender intrakranieller Prozesse prolabierer. Andererseits scheint es, dass die monorhythmische, frontale Deltaaktivität, welche oft kurze Zeit nach frontaler Leukotomie angetroffen wird, am besten dadurch erklärt wird, dass die konsekutiv zur Leukotomie auftretende Degeneration und Gliose im dorsomedialen Thalamuskern zu einem vorübergehenden Reizzustand führt, welcher für diese frontale Aktivität verantwortlich ist.

I would like to express my thanks to Dr. W. A. Cobb for his advice and criticism throughout the preparation of this paper and to Miss Jean Fraser for her invaluable assistance.

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ELECTROENCEPHALOGRAPHIC ABNORMALITIES IN ADDITION TO BILATERALLY SYNCHRONOUS 3 PER SECOND SPIKE AND WAVE ACTIVITY IN PETIT MAL [1]

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According to Temkin (1945) the terms "grand mal" and "petit mal" were used in Parisian hospitals as early as 1815 to describe "severe and slight" epileptic attacks. A further classification was necessary with the introduction of the term "absence" by Calmeil in 1824. "The fully developed fit was distinguished by the name of "grand mal"; those cases characterized by a passing mental confusion without any other definite physical symptoms were easily characterized as "absences"; while "petit mal" remained a convenient term to comprise the great variety of not fully developed attacks." (Temkin 1945). In 1879 Jackson, employing the terms petit mal and grand mal to differentiate the slight from the severe epileptic attacks, stated that in petit mal "the effects of the discharge are limited to the highest centers". He thought "that there may be a discharge strong enough to abolish consciousness, and yet not strong enough to produce any or very slight, peripheral effects". Gowers (1881) used the words "minor attacks" and petit mal interchangeably. He described the most common form of petit mal as a "transient loss of consciousness without conspicuous convulsion". Both Jackson and Gowers included in their petit mal classification episodes which would now be called "temporal lobe" seizures.

With the advent of electroencephalography many of the ill-defined "slight attacks" were noted to be associated with bilaterally synchronous 3 c/sec. spike and wave activity. This group was set apart and has come to be known as the true "petit mal" variety while the remainder of the "slight attacks" have been found to be psychomotor, minor motor and sensory attacks as well as a variety of other types. In an effort to clarify this situation Gibbs and Gibbs (1952) have defined petit mal as brief (2-15 sec.), frequent (6 to 100 per day) attacks of impaired consciousness, rarely preceded by an aura but associated with one or more of the following manifestations: staring, rhythmical blinking, nodding of the head, jerking of the arms or sudden loss of posture and characterized electroencephalographically by 3 per second spike and wave discharges. Another electroencephalographic feature of petit mal is the sudden appearance and disappearance of the bilaterally synchronous activity, often against a normal background.

In examining EEG's of patients with petit mal we have been interested by cases where focal or asynchronous diffuse abnormalities occur between seizures and where the seizure discharges themselves are asymmetrical. For this reason we reviewed a series of 100 consecutive cases of petit mal studying particularly the abnormalities in the background activity of the EEG and attemping to correlate these with clinical features such as abnormal neurologic signs, mental retardation and other seizure types. All patients had EEG examinations at the Neurological Institute between May 1953 and July 1956.

In each instance the diagnosis was established by observing a clinical attack of petit mal which occurred simultaneously with generalized 2.5 to 3.5 per sec. spike and wave activity. Many of the patients had a history of grand mal attacks in addition to petit mal.

[1] Presented in part at the Fourth International Congress of EEG and Neurophysiology, Brussels 1957.

Some patients had serial tracings taken over a period of years, but in most cases only one record was obtained. Additional clinical information was acquired by reviewing hospital records.

RESULTS

Analysis of Electroencephalograms

Of the 100 cases reviewed there were 51 in which all abnormal activity was bilaterally synchronous. Of the remaining 49 cases, 35 showed focal or lateralized abnormalities and 14 had diffuse asynchronous abnormalities (table I). The cases were grouped as follows:

A. Bilaterally synchronous or "classic" group (51 cases): Included in this group were all those tracings in which the background activity was essentially normal. Bursts of paroxysmal activity were always bilaterally synchronous and were not consistently restricted to any particular portion of the hemispheres. When 3 c/sec. spike and wave bursts occurred their onset was bilaterally symmetrical (fig. 1).

B. Focal or lateral abnormalities (35 cases): Under focal abnormalities were included those tracings in which the background

TABLE I

Focal or Lateral Abnormalities — In the Electroencephalograms of 35 Patients with Petit Mal.

Group B.	
Slow wave foci	4
Spike or spike and wave foci	6
Bioccipital slow wave or spike and wave activity	7
Inconstant focal spike and wave discharge	2
Unilateral onset of seizures discharge	2
Slow activity predominantly unilateral	6
Spike or spike and wave activity predominantly unilateral	7
Slow activity and spiking predominantly unilateral	1
Total	35

Diffuse Abnormalities — In the Electroencephalograms of 14 Patients with Petit Mal.

Group C.	
Slow	8
Diffuse spiking	4
Slow with diffuse spiking	1
Changing slow wave foci	1
Total	14

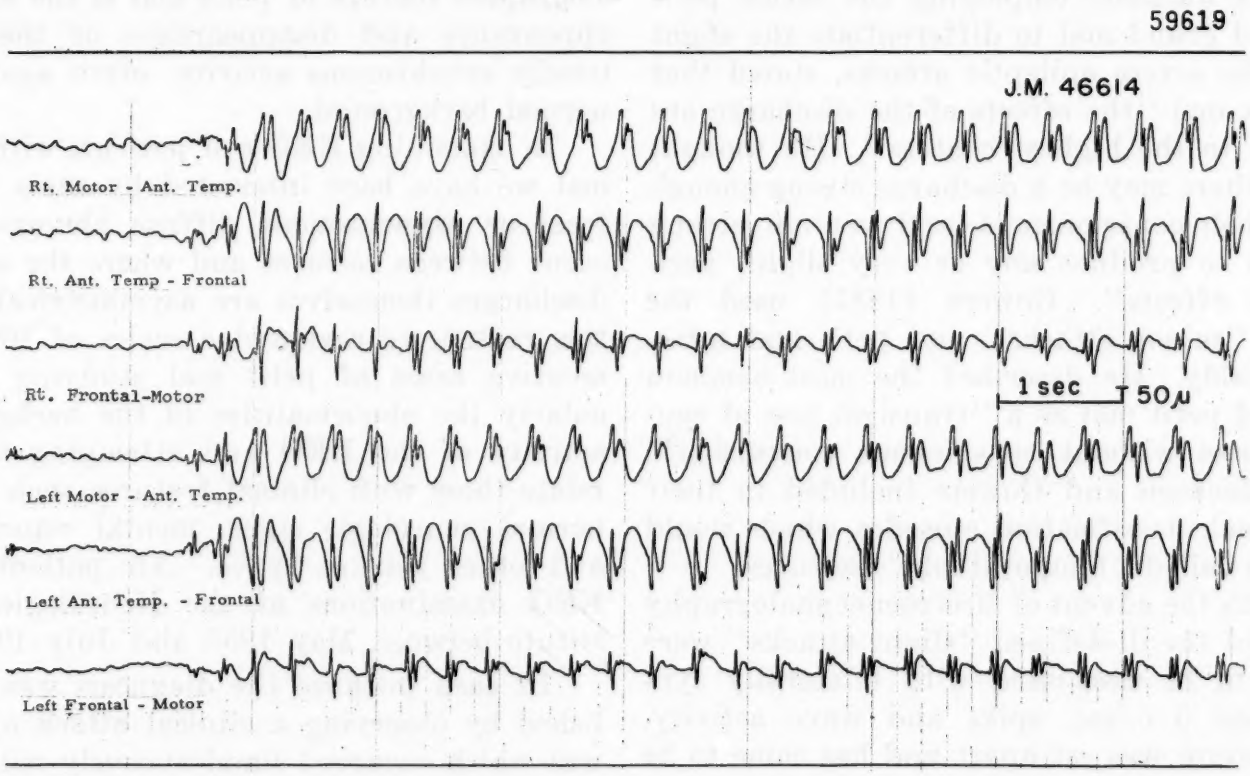


Fig. 1

Recording of a petit mal attack in a 14 year old boy who also has grand mal seizures. During petit mal spells the patient is unresponsive, turns his head and eyes to the right and raises his right hand or both hands to his head.

activity contained a focus of spike, slow wave, or spike and wave activity. If bursts of paroxysmal activity consistently occurred in one portion of a cerebral hemisphere, the case was also included. In the group of lateral abnormalities were placed those tracings in which the petit mal discharges originated on one side, or where other abnormalities including paroxysmal activity were lateralized to one hemisphere (fig. 2 to 6).

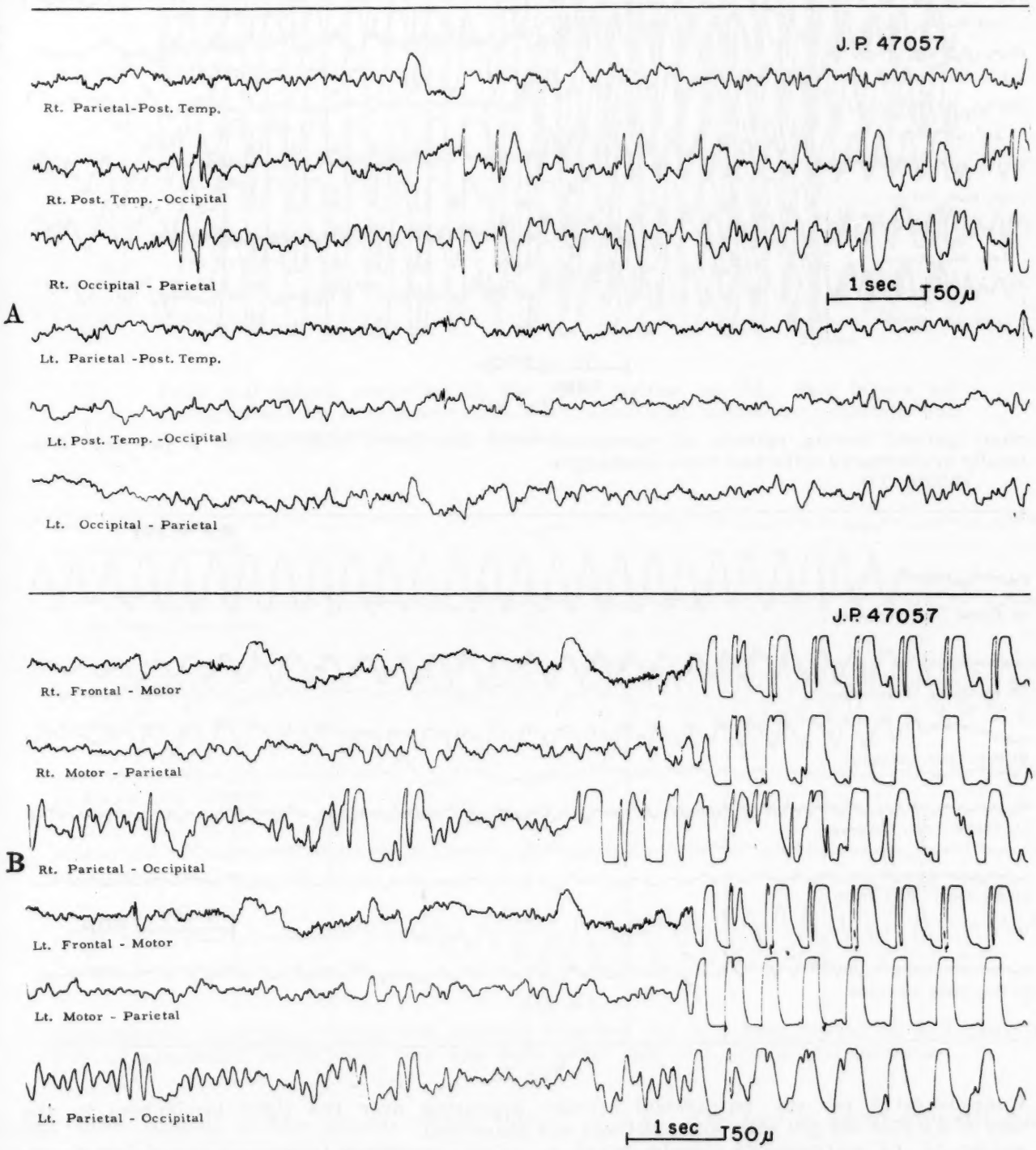


Fig. 2A

This is an interseizure record of a 4½ year old boy who has only petit mal attacks. A prominent spike and slow wave focus had been present in the right occipital area for over a year.

Fig. 2B

Same patient as 2A during onset of attack of unresponsiveness. Bilaterally synchronous spike and wave discharges are preceded by spike and slow wave activity in the right occipital area.

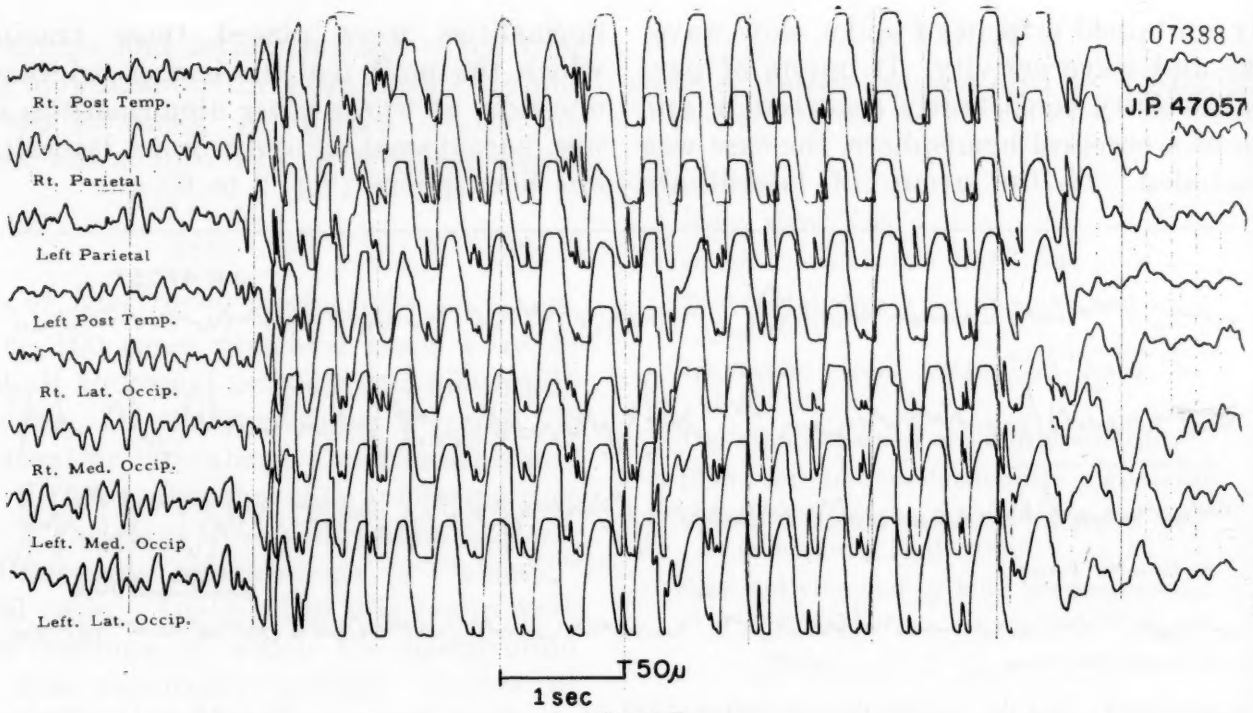


Fig. 2C

Same patient having episode of unresponsiveness associated with 2½ to 3 per sec. bilaterally synchronous spike and wave discharges.

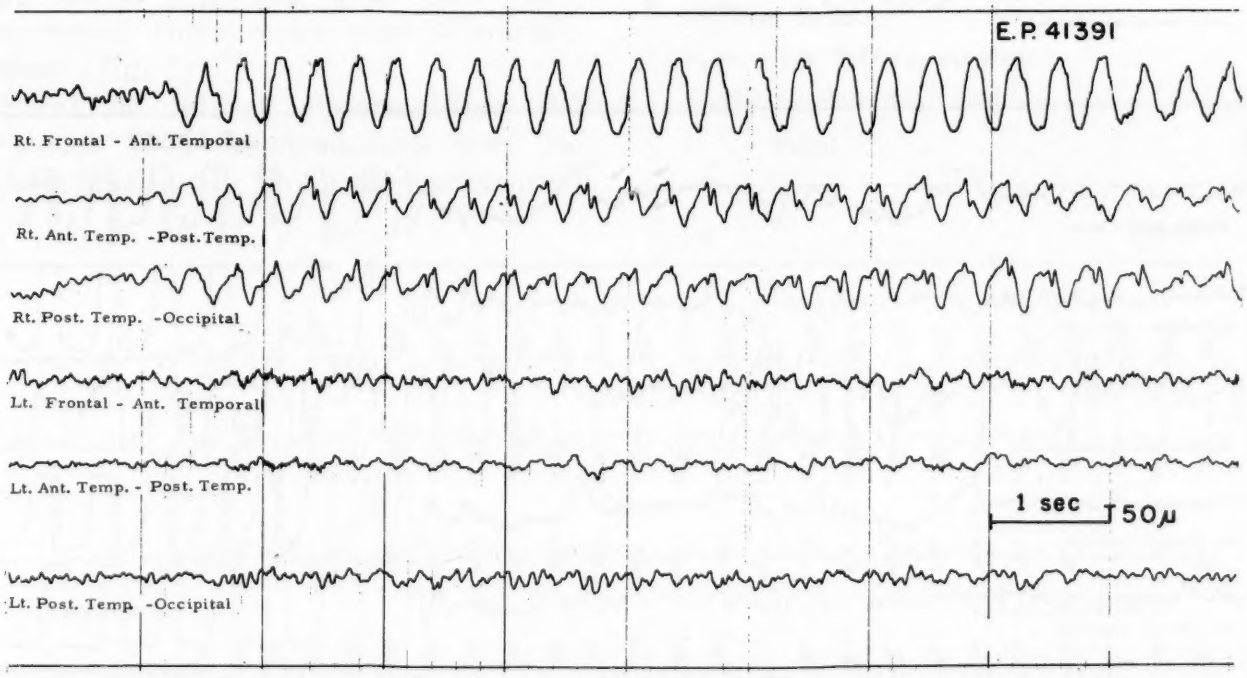


Fig. 3A

Interseizural 3 per sec. paroxysmal activity appearing over the right hemisphere in the case of a 9 year old girl with both petit mal and grand mal.

C. Diffuse abnormalities (14 cases) : This group included those cases in which the background activity contained abnormalities which could not be considered bilaterally synchronous, focal or lateral in distribution. Such abnormalities as asynchronous diffuse spiking or slow activity and changing foci were included in this group. If a tracing was considered immature for its age group it was included in the above grouping (fig. 7 and 8).

Some records contained both focal and diffuse abnormalities. In these instances the

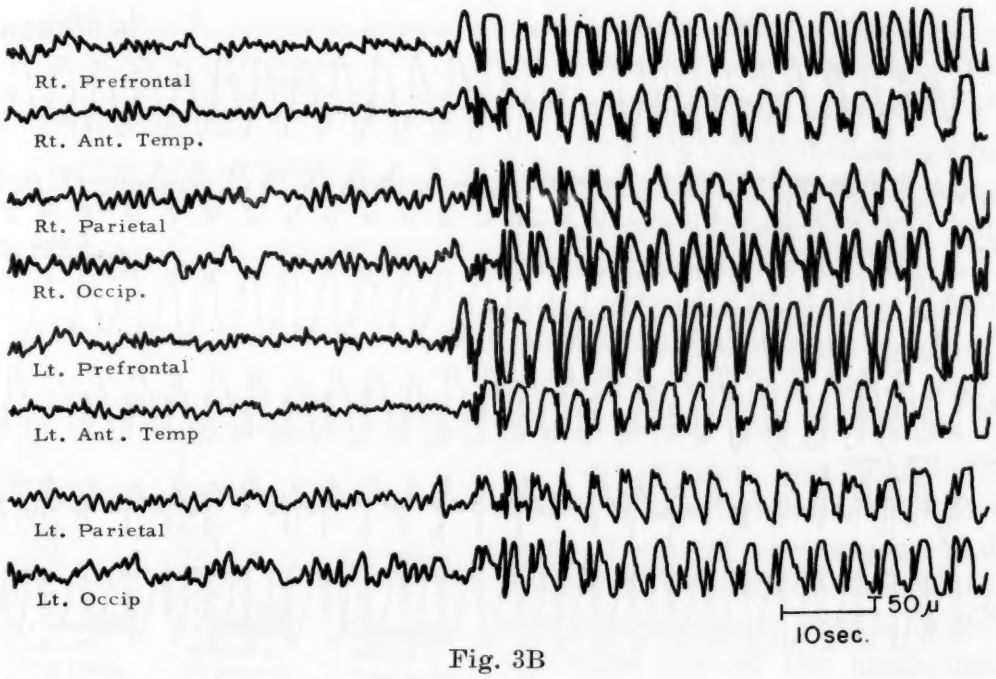


Fig. 3B

Petit mal attack occurring in the same patient as 3A. Her lapses are characterized by unresponsiveness with occasional masticatory activity and purposeless movements of the hands.

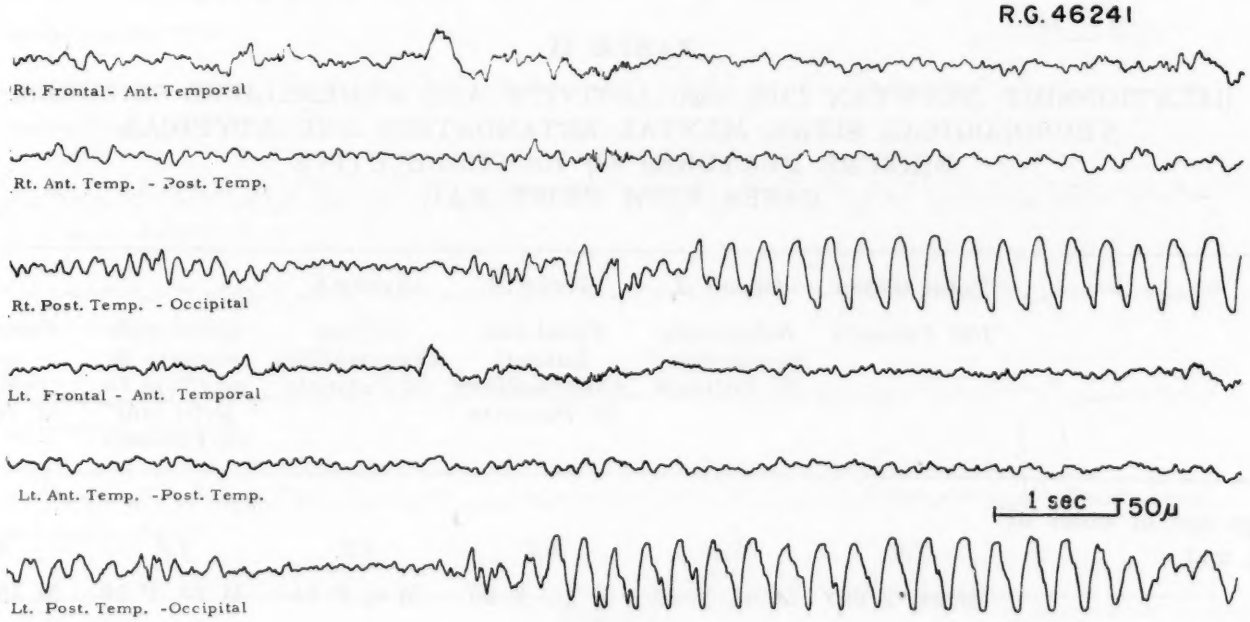


Fig. 4A

Interseizural bioccipital paroxysmal activity observed for a 2 year period in a 7 year old boy of subnormal intelligence who has both petit mal and grand mal seizures.

records were placed in the group which best described the most abnormal feature.

Analysis of case histories (tables II and III):

Sex: Sixty-two of the total group of 100 patients with petit mal were female. In group A the number of each sex is about equal. In group B there is a preponderance of females while group C is composed only of females.

Age: The age at onset of petit mal ranged from about 18 months to 15 years with an average of 7.0 years. The age at the time of the first petit mal or grand mal attack did not differ significantly among the three groups. In five instances neither the patient nor the family were aware of the petit mal episodes and they were first noted when an EEG was recorded for other reasons. In most

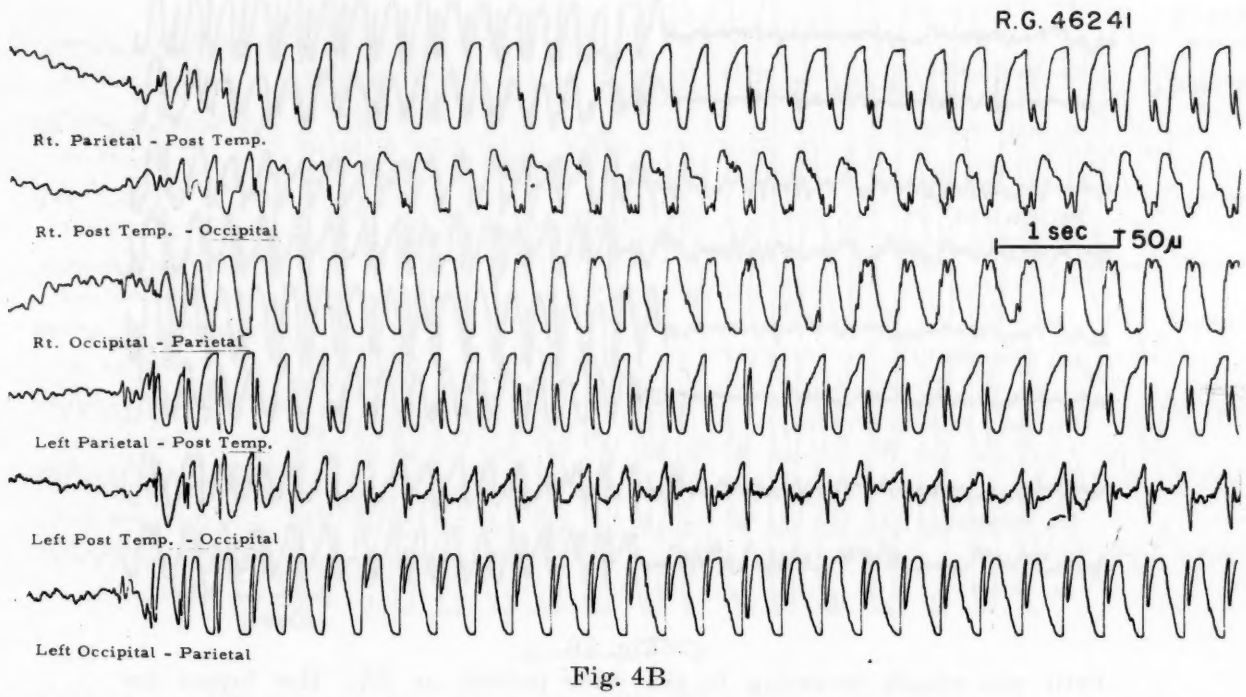


Fig. 4B

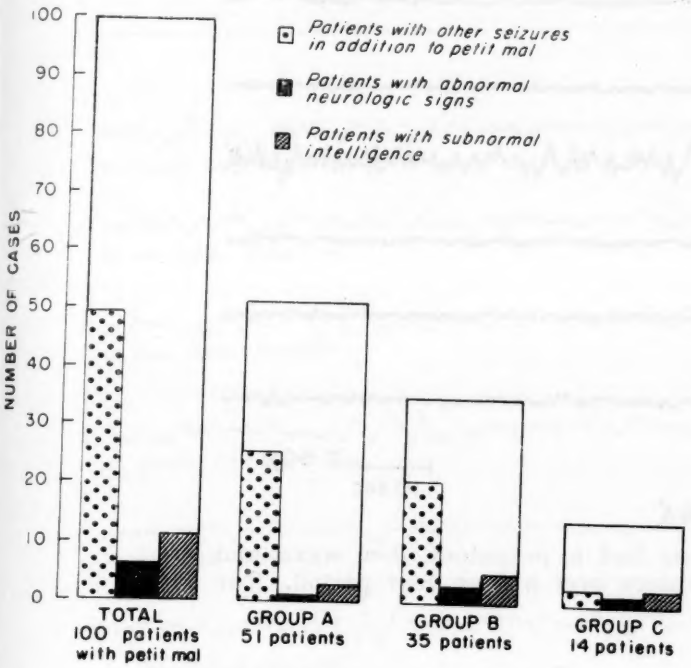
Typical petit mal attack in the same patient. During recorded spells he was unresponsive, put his hands to his head, moved his feet and had masticatory movements.

TABLE II

RELATIONSHIP BETWEEN THE EEG ACTIVITY AND GENERALIZED SEIZURES, NEUROLOGICAL SIGNS, MENTAL RETARDATION AND ATYPICAL SEIZURE FEATURES IN 100 CONSECUTIVE CASES WITH PETIT MAL

	Total Group *100 Patients*	*Group A* *Bilaterally Symmetrical 51 Patients*	*Group B* *Focal and Lateral Abnormalities 35 Patients*	*Group C* *Diffuse Abnormalities 14 Patients*	*Cases with seizures in addition to petit mal 49 Patients*	*Cases with only petit mal 51 Patients*
Average age at onset of petit mal	7.0	7.5	6.5	6.2	7.4	6.6
Sex	M 38, F 62	M 25, F 26	M 13, F 22	M 0, F 14	M 20, F 29	M 18, F 33
Number with other seizures in addition to petit mal	49	25	21	3	49	
Average age at onset of seizures other than petit mal	7.7 yrs.	8.7 yrs.	6.4 yrs.	8.6 yrs.	7.7 yrs.	
Number with neurologic signs	6	1	3	2	5	1
Number with sub-normal intelligence	11	3	5	3	6	5
Number with atypical manifestations of petit mal	40	18	16	6	16	24

TABLE III



cases when other types of seizures were present their onset was at an earlier age than that of petit mal.

Heredity: Nineteen of the total group had close relatives (parents, grandparents, siblings, uncles or aunts) who had a history of convulsive seizures. In the 51 patients with pure petit mal there was a family history of seizures in 12. In the remaining 49 having both petit mal and other seizure types the family history was positive in seven.

Neurological and Laboratory Examinations: Six patients in the entire group had signs of central nervous system disease on neurologic or laboratory examination other than moencephalogram, gave a history of injury to the right side of the head and, in addition,

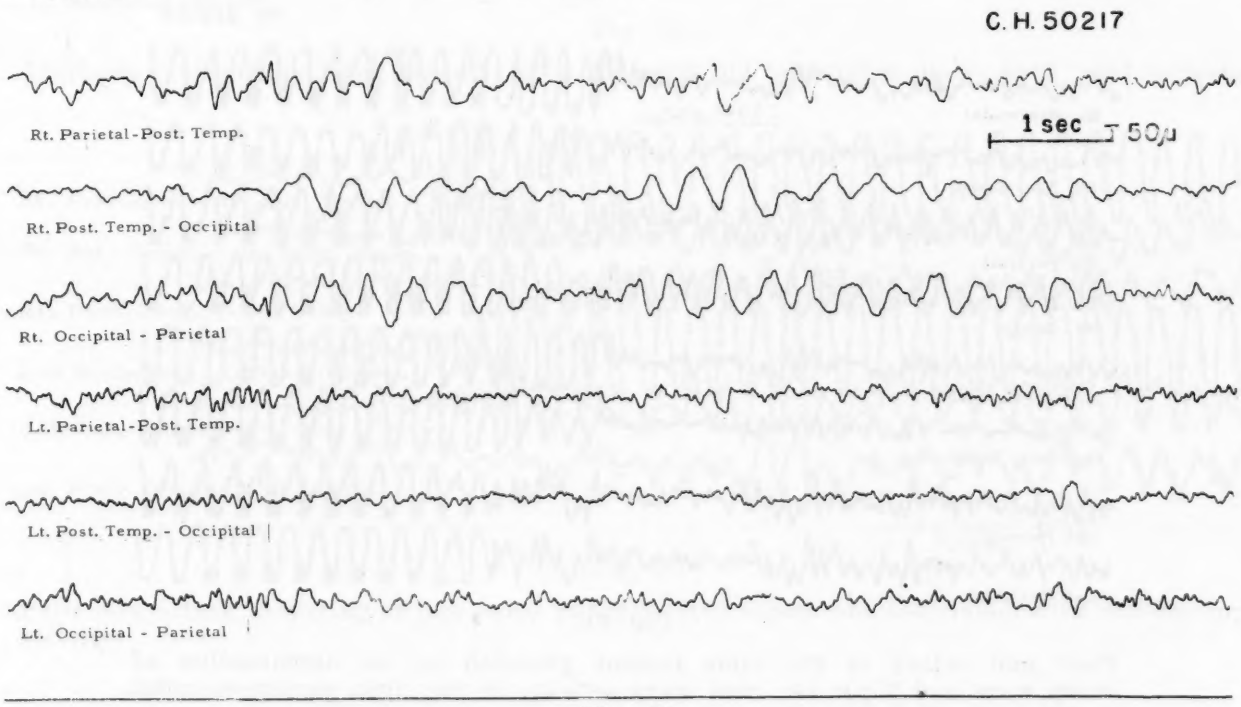


Fig. 5A

Interseizural right occipital and temporal slow wave focus in the tracing of a 13 year old girl with both grand mal and petit mal. During grand mal attacks the motor activity is greater on the left than on the right.

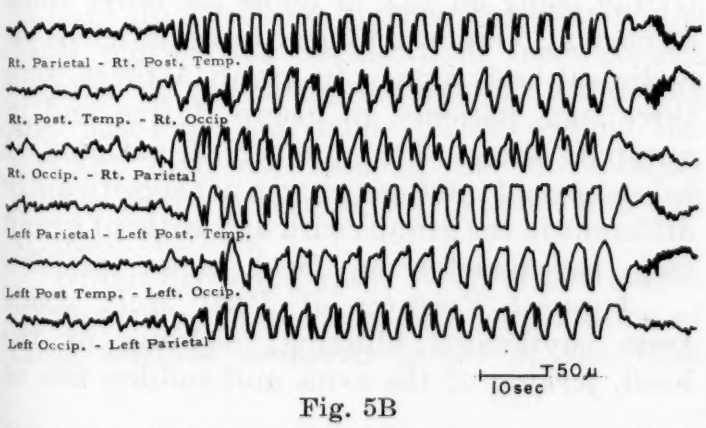

Rt. Parietal - Rt. Post. Temp.
Rt. Post. Temp. - Rt. Occip.
Rt. Occip. - Rt. Parietal
Left Parietal - Left Post. Temp.
Left Post Temp. - Left. Occip.
Left Occip. - Left Parietal
50μ
10sec

Fig. 5B

Typical petit mal attack occurring in the same patient.

EEG. In group A one patient had an unexplained persistently elevated cerebrospinal fluid protein of 84 mg. per 100 ml. Physical and neurologic examinations as well as a pneumoencephalogram were normal. In group B one patient was found to have hyperactive reflexes and bilateral Babinski signs while another patient had an elevation of spinal fluid protein to levels of 122 mg. per 100 ml. which could not be explained. A third patient, showing an enlargement of the atrium of the right lateral ventricle by pneu-

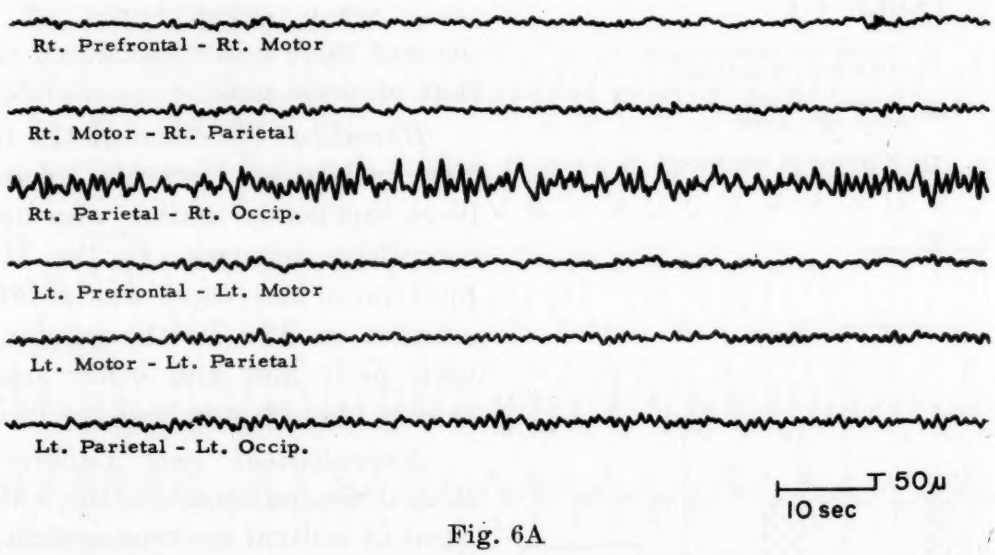

Rt. Prefrontal - Rt. Motor
Rt. Motor - Rt. Parietal
Rt. Parietal - Rt. Occip.
Lt. Prefrontal - Lt. Motor
Lt. Motor - Lt. Parietal
Lt. Parietal - Lt. Occip.
50μ
10 sec

Fig. 6A

Tracing of an 11 year old boy who has had a persistent slow wave and sharp wave focus in the right occipital area over a four year period. The patient has petit mal but not grand mal.

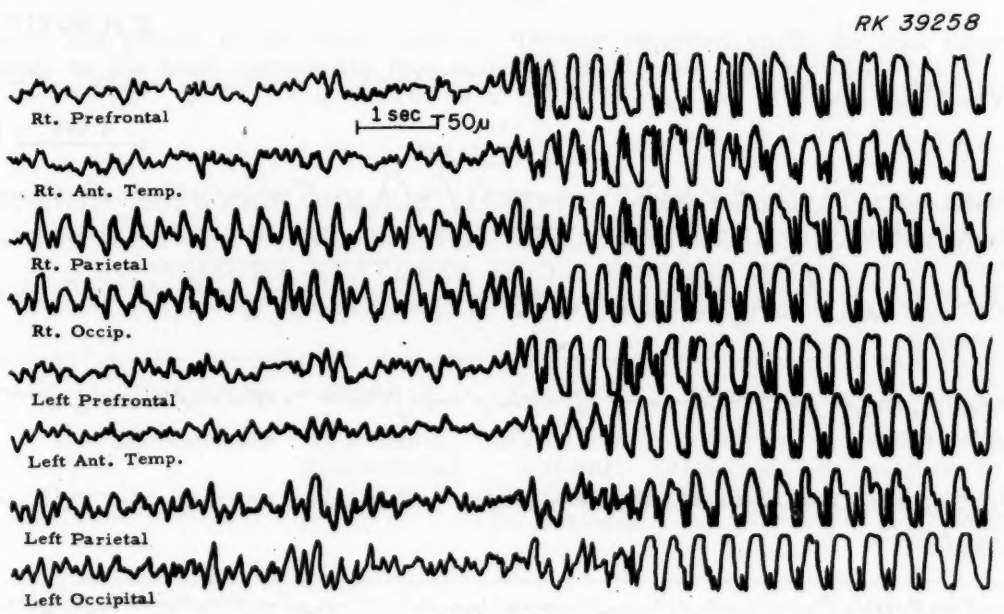


Fig. 6B

Petit mal attack in the same patient preceded by an accentuation of sharp wave and 3 per sec. slow wave activity in the right parieto-occipital region.

had had two psychomotor attacks progressing to generalized major seizures. In group C two patients showed evidence of cerebellar dysfunction in the form of ataxia and terminal tremor. Although medicinal side effects were considered, in neither instance was an explanation for the cerebellar features found. All but one of the patients with abnormal neurologic findings had grand mal or psychomotor seizures.

Mental Status: Eleven of the total group were below normal in intelligence. Ten of these were evaluated by formal psychological testing using an I.Q. of 80 as the lower limit of normal. One was judged to be deficient on a clinical basis alone. In group A there were three such patients, in group B five and in group C three. The number of patients of below normal intelligence was not significantly different in the groups with and without grand mal, psychomotor or focal motor attacks.

Atypical Features of Petit Mal: Aside from rhythmical blinking, nodding of the head, jerking of the arms and sudden loss of

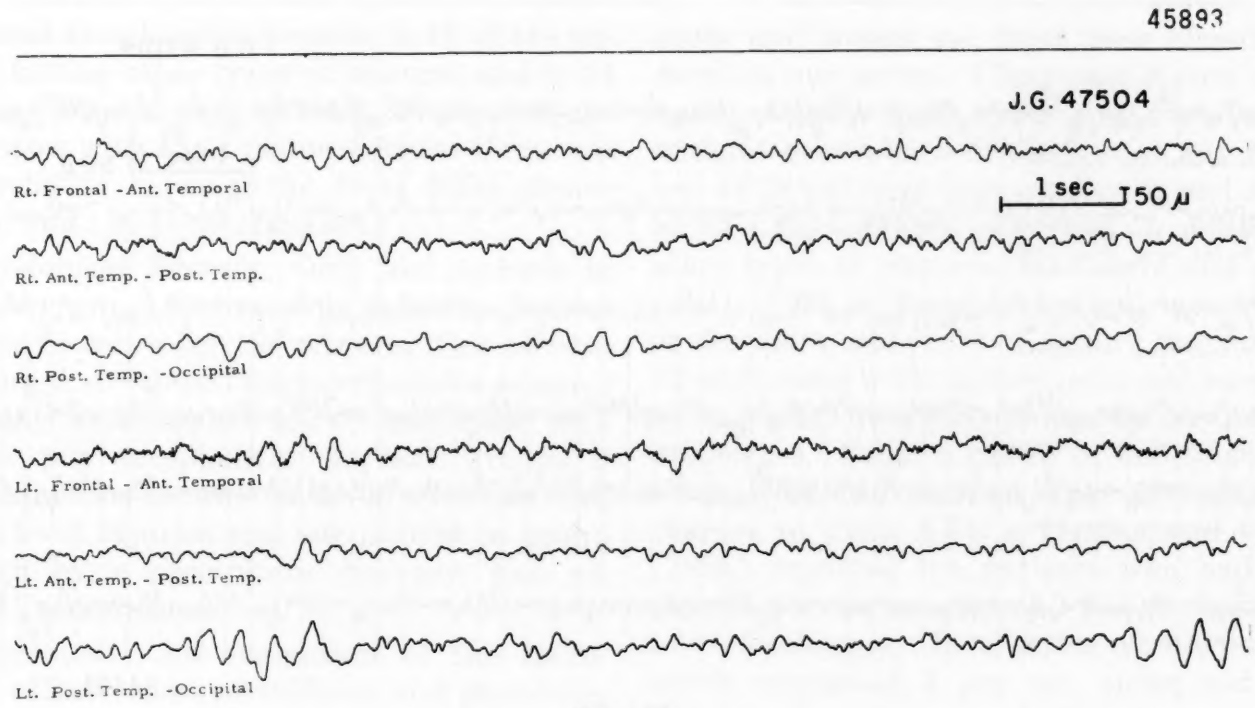


Fig. 7A

Diffusely abnormally slow record of a 9 year old girl with only petit mal attacks.

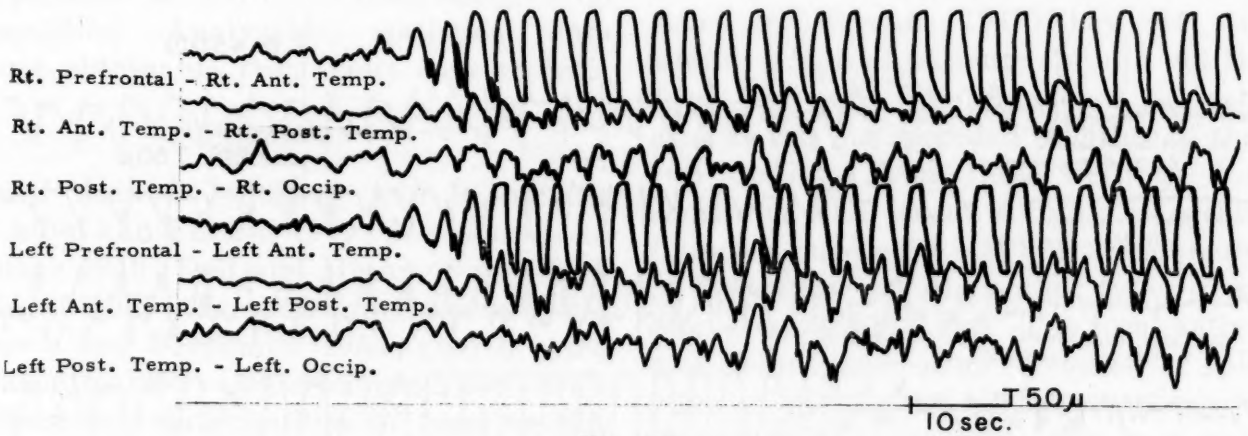

Rt. Prefrontal - Rt. Ant. Temp.
Rt. Ant. Temp. - Rt. Post. Temp.
Rt. Post. Temp. - Rt. Occip.
Left Prefrontal - Left Ant. Temp.
Left Ant. Temp. - Left Post. Temp.
Left Post. Temp. - Left. Occip.
50 μ
10 sec.

Fig. 7B

Petit mal attack occurring in the same patient. Her lapses are associated with masticatory activity.

posture, 40 of the cases had other manifestations not usually considered to be associated with petit mal. These patients were observed to have lip smacking, purposeless coordinated hand movements, vocalization, incontinence, turning of the head, walking or wandering and post-ictal confusion. There was no significant difference among the three EEG groups in the percentage of patients who had atypical features.

Other Seizure Types: Generalized major, psychomotor, focal motor or a combination of these seizures occurred in 49 of the total group in addition to the petit mal attacks. There were 25 patients with these types of seizures in group A, 21 in group B and three in group C. In all but seven instances the seizures were of the grand mal variety. Of these seven patients three had psychomotor and four had focal motor seizures. Two patients had both grand mal and psychomotor attacks. In 15 instances the initiation of petit mal attacks followed the onset of the other types of seizures. In 12 cases both types of spells began at about the same time and in ten patients the first generalized major, psychomotor or focal motor at-

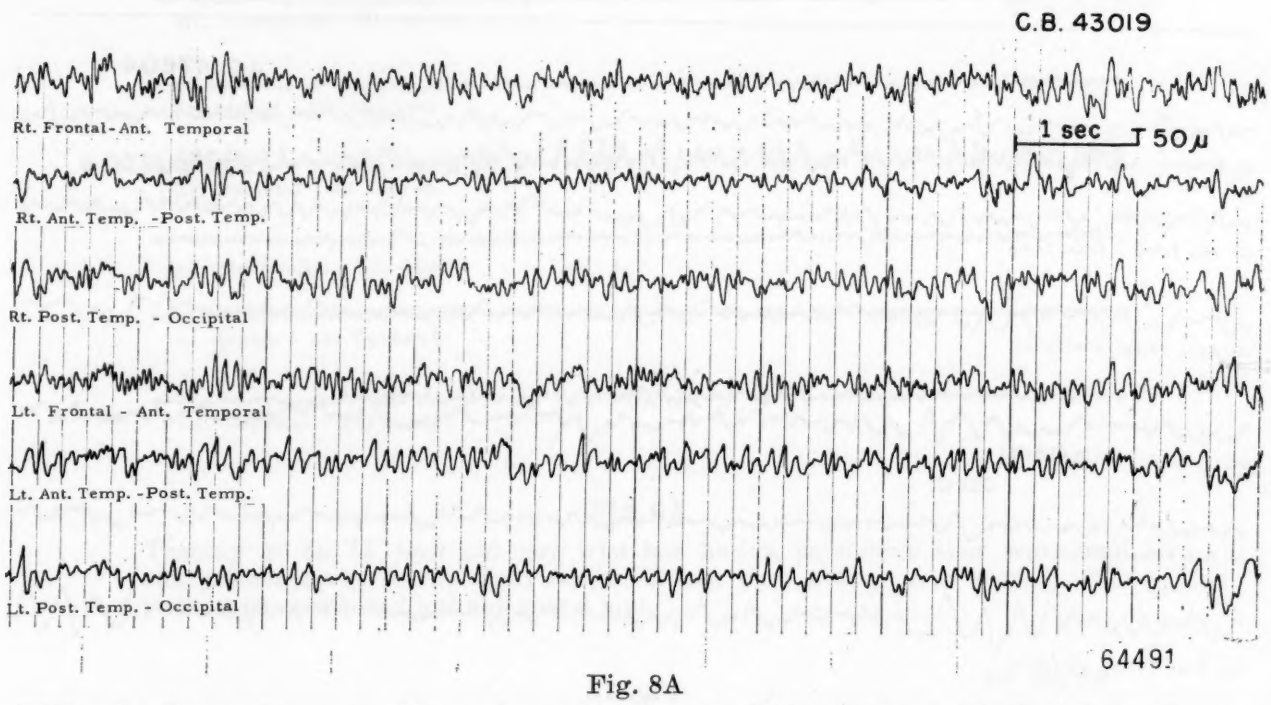


Fig. 8A

Diffusely abnormal record with random spikes over both hemispheres. Patient is a 12 year old girl with only petit mal.

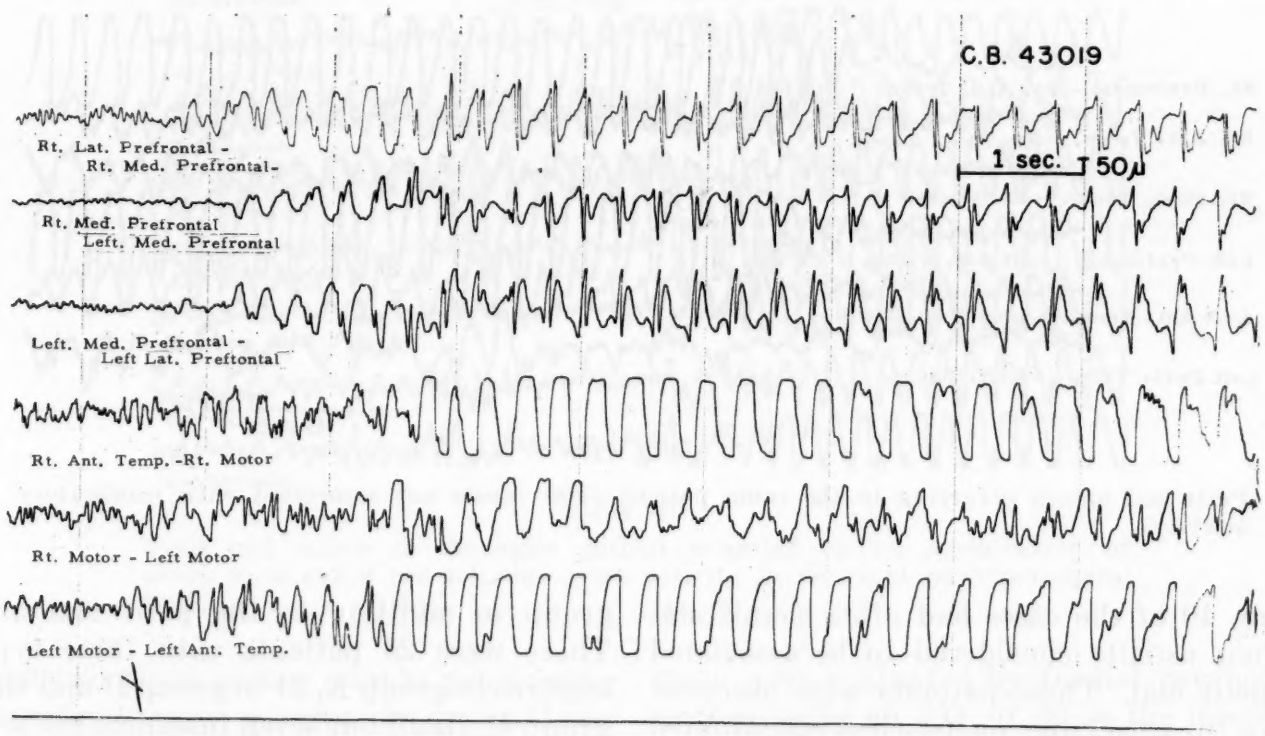


Fig. 8B

Petit mal attack occurring in the same patient. During her attack she is unresponsive, mumbles and licks her lips.

tack followed the onset of petit mal. In 12 cases the age of onset of petit mal could not be ascertained. Abnormal neurologic findings were present in five of the patients having other types of seizures associated with petit mal and in only one of the group with petit mal alone. There were six patients with mental deficiency in the group with generalized major, psychomotor or focal seizures and five in the group with pure petit mal. Atypical

petit mal attacks were present in 16 of the patients having other types of seizures and in 24 of those without such attacks. In three of the four cases with focal motor seizures there was a correlation between the focal EEG abnormality and the clinical attack.

Etiological Factors: Only six patients in the entire group had possible causative factors in their histories for the seizures. One patient in group A developed his psychomotor seizures following an illness, at age 9, compatible with chicken pox encephalitis. In both groups B and C there were two patients who had had severe head injuries and one patient in group C, born by a precipitous delivery, had required resuscitation.

Treatment: An evaluation of the therapeutic effectiveness of tridione and paradione was attempted in the three categories in order to determine the effectiveness of these drugs in the presence of diffuse or focal background abnormalities. Analyzable, statistical data were not obtainable from most case records.

DISCUSSION

Many authors (Jasper and Kershman 1941; Allen and Forster 1949; Jewesbury and Parsonage 1949; Dell and Hecan 1951; Clark and Knott 1955; Terzian and Cecotto 1955; Morosseva and Bergamini 1953; Ogden, Aird and Garoutte 1956; Calderón and Paal 1957), have described abnormalities of focal or diffuse nature in the EEG's of patients with petit mal. In some instances reports are difficult to analyze as they were not made primarily for study of this point. In an analysis of 17 cases of "pure" petit mal Jasper and Kershman (1941) found local spikes in one record while in 40 cases with both petit mal and grand mal they noted five with diffuse abnormalities. Gibbs and Gibbs (1952) observed focal larval petit mal discharges in 84 cases and focal spikes in 15 of 137 cases with only clinical petit mal attacks. In a similar group of 320 with both petit mal and grand mal there were 264 with focal larval petit mal discharges and 43 with focal spikes. The larval petit mal discharges were apparently only transiently present in various cortical areas and would not have been classified as focal in our series. Clark and Knott (1955) noted strictly focal spike and wave activity without generalized discharges at any time in two of 28 patients with pure petit mal and six of 95 patients with petit mal in addition to other types of seizures. Marosseva and Bergamini (1953) reported lateralized larval bursts or the unilateral onset of seizure discharges in 12 of 41 cases with clinical petit mal associated with typical 3 to 3.5 per sec. spike and wave discharges. From a group of 400 seizure patients with well defined spike and wave discharges in their EEG's Terzian and Cecotto (1955) reported ten patients who had asynchronous or asymmetrical 3 per sec. spike and wave discharges. In a series of 100 tracings which contained 3 per sec. spike and wave activity Jewesbury and Parsonage (1949) found three cases in which the spike and wave activity was localized to the frontal regions. Allen and Forster (1949), however, studied a similar group of patients and did not find any focal activity. The incidence of petit mal attacks was not recorded in either of the latter two studies. From these writings it can be concluded that focal activity is occasionally found in pure petit mal but is seen more often in the patient who has other types of seizures complicating petit mal. The focal activity has been found most often to consist of spike and wave or rhythmical slow wave discharges although focal spikes have also been noted.

In our series 49 of 100 patients with petit mal were found to have focal and diffuse asynchronous electroencephalographic abnormalities and more than two thirds of these were focal or lateral. The presence of other types of seizures in addition to petit mal, however, did not increase the frequency of the focal or diffuse abnormalities.

Though the cases of Gibbs and Gibbs (1952) showed no difference in sex distribution, the series of Lennox and Davis (1950) revealed that of the patients with 3 per sec. spike and wave activity 60 per cent were female. In our own series 62 per cent were female, their preponderance in groups B and C being unexplained.

Lennox and Davis (1950) found that 23.3 per cent of patients with 3 per sec. spike and wave activity had close relatives with a history of convulsions which is similar to our own figure of 19 per cent.

Six patients of our entire group showed signs of central nervous system damage on neurologic or laboratory examinations other than EEG. Five of these patients were in groups B and C and all but one had either grand mal or psychomotor attacks. Gibbs and Gibbs (1952) found 5.4 per cent of patients with only petit mal and 7.4 per cent of those with both petit mal and grand mal to have abnormal neurologic signs and symptoms. Our data tend to suggest some concurrence between the presence of grand mal or psychomotor seizures, background EEG abnormalities and brain damage in patients with petit mal.

Of the 11 patients having some degree of mental deficiency eight were in groups B and C. Of the 14 cases in group C alone, there were three whose intelligence was below normal. Similarly Gibbs and Gibbs (1952) found 10.0 per cent and Lennox and Davis (1950) 9.0 per cent of their cases to be impaired. The rather high incidence of mental retardation suggests that a common factor such as underlying brain damage may be accountable for this situation. The fact that the EEG's in the majority of these patients were classified in groups B and C suggests some correlation between the EEG abnormalities, mental retardation and possible brain damage. There was, however, no difference between the groups with and without grand mal and psychomotor seizures in regard to the number of patients with retardation.

The occurrence of atypical features during attacks of petit mal caused difficulty in diagnosis and some patients were at first thought to have psychomotor seizures. Penfield and Jasper (1954) classify such patients as having petit mal automatisms. In their experience this occurs infrequently, but we have observed this phenomenon in about 40 per cent of our cases. The lack of correlation of these atypical features with any focal, lateral or diffuse EEG abnormalities would tend to indicate that they are an intrinsic part of the petit mal attack and probably not due to focal cortical involvement.

The presence of generalized or psychomotor seizures in about half of the patients with petit mal (49 of 100) correlates well with the findings of Lennox and Davis (1950) and Gibbs and Gibbs (1952) who reported that about 55 per cent of their petit mal cases were complicated by grand mal or psychomotor attacks.

Focal or diffuse EEG abnormalities were not significantly more frequent in patients who had generalized or psychomotor seizures. In three of the four patients with focal motor accentuations to their seizures there was an appropriate focal abnormality in the EEG.

The origin of the bilaterally synchronous 3 per sec. spike and wave discharges is thought by many to be in deep midline structures of the brain. This idea is supported by the experimental work of Jasper and Droogleever-Fortuyn (1947) and Hunter and Jasper (1949) who succeeded in eliciting bilaterally synchronous 3 per sec. spike and wave discharges by thalamic stimulation. The direct recording from the thalamus of patients with petit mal by Williams (1953) lent further support to this idea. The failure to find constant pathological changes in the cerebral hemispheres (Meyer 1958) has also led investigators away from the cortex and into the brain stem in their search for mechanisms underlying petit mal. Because of the possible origin of the petit mal discharges in the deep midline structures considerable stress has been placed on the importance of the bilateral synchrony of the abnormal discharges.

An asymmetry of the spike and wave discharges over the two hemispheres, however, can be detected by special recording equipment in some "classical" cases of petit mal which appear to be bilaterally synchronous when tested on the usual paper writing electroencephalograph. Using photographic paper moving at speeds of 10 to 50 cm. per second Penfield and Jasper (1954), Cohn (1954) and Ogden, Aird and Garoutte (1956) noted dif-

ferences in synchrony of 10 to 20 msec. between the two hemispheres. In an attempt to explain the more prominent asymmetries such as the type we have described above, Terzian and Cecotto (1955) have postulated three alternatives:

1. Abnormal discharges having their origin in medial thalamic structures may evoke asymmetrical or asynchronous cortical activity because of differences in the responsiveness of the two hemispheres.

2. The exciting focus may be subcortical but lateralized to one side of the midline as demonstrated by Jasper (1949) in stimulation of the thalamic reticular system.

3. A cortical focus, in addition to giving evidence of its own presence, may produce bilateral discharges by means of subcortical or diffuse projections. An additional factor to be considered is that discharges which originate in midline structures may have asymmetrical projections.

In our material there are two cortical foci which particularly appear to be the trigger zones for bilateral 3 per sec. spike and wave discharges (fig. 2 and 6). In one patient a spike and wave focus has been present in the right occipital area for at least one year. Immediately preceding the development of bilaterally synchronous discharges the spike and wave activity in the focus is intensified. This suggests that the discharging cortical focus at times projects to deep midline structures and causes the initiation of discharges from these areas which in turn results in the appearance of spike and wave discharges over both hemispheres.

Another patient demonstrating a similar situation is shown in fig. 6. In this case the focus was known to be present for four years. In other instances in which slow wave, spike or spike and wave foci were present a similar accentuation of these discharges immediately preceding a petit mal attack was not observed.

Ogden, Aird and Garoutte (1956) reported the presence of a slow wave focus in the right temporal and central areas in a patient with both petit mal and left adversive or Jacksonian seizures. In a high percentage of runs the spike and wave discharges started on the right side one or two seconds before the left. The authors felt that a stream of impulses from the focus might affect a paramesial regulatory or pacemaking mechanism which could cause the asynchronous appearance of the bilateral spike and wave discharges. Further study has led Aird and Garoutte (1958) to feel that this pacemaker or regulating center of cortical rhythms may be located either in the posterior hypothalamic-subthalamic area or in the closely adjacent reticular formation of the upper brain stem.

The possibility of persistent foci being produced by discharges originating from paramesial deep structures particularly in the case of a rhythmical slow wave focus, is also to be considered. This mechanism can be extended to instances were the spike and wave discharges appear over one hemisphere. As suggested by Terzian and Cecotto (1955) the over-responsiveness of one hemisphere or one area to discharges projected from deep midline centers may also account for these findings. In the case of the diffusely asynchronous abnormal interseizural records it is conceivable that the abnormal cortical discharges fire the deep midline structures to activate the bilateral 3 per sec. synchronous discharges. It is also possible that independent discharging areas are present in both the cortex and subcortical structures.

SUMMARY

1. In 100 consecutive patients in whom clinical petit mal attacks were associated with 3 per sec. spike and wave activity the presence of focal, lateral and diffuse EEG abnormalities was studied.

2. In 51 cases the background activity of the EEG was essentially normal. In 35 cases focal or lateralizing abnormalities were present. In 14 cases the background activity was diffusely abnormal.

3. Sixty-two patients were female. The average age of onset of petit mal was seven years. Nineteen had close relatives with a history of convulsions. Six patients had abnormal neurologic findings. Eleven were low

in intelligence. Forty patients had atypical features to their seizures. Forty-nine had other types of seizures in addition to petit mal. Possible etiologic factors were present in the histories of only six patients.

4. Correlations were noted between the presence of EEG abnormalities other than synchronous 3 per sec. spike and wave activity and (*a*) mental retardation and (*b*) abnormal findings on neurologic examination.

5. The possible meaning of the high incidence of abnormalities, other than 3 per sec. spike and wave discharges, in terms of the genesis of petit mal activity is discussed.

RÉSUMÉ

1. On a étudié les anomalies EEG focales, latéralisées et diffuses chez 100 patients consécutifs présentant des crises cliniques de petit-mal associées à une activité pointe-onde à 3 c/sec.

2. Chez 51 cas l'activité de fond de l'EEG était essentiellement normale. Chez 35 cas des anomalies focales ou latéralisantes étaient présentes. Chez 14 cas l'activité de fond était anormale de façon diffuse.

3. Soixante-deux des patients étaient de sexe femelle. L'âge moyen de début du petit-mal était 7 ans. Dix-neuf patients avaient des parents proches avec une histoire convulsive. Six patients avaient des signes neurologiques anormaux. Onze patients étaient des arriérés-mentaux. Quarante patients avaient des manifestations atypiques lors de leurs crises. Quarante-neuf avaient d'autres types de crises en plus du petit-mal. Des facteurs étiologiques possibles étaient relevés dans les antécédents de seulement six patients.

4. On a noté des correlations entre la présence d'anomalies EEG autres que l'activité pointe-onde synchrone à 3 c/sec. et *a*) l'arriération mentale, *b*) les découvertes anormales dans l'examen neurologique.

5. On discute la signification possible de l'incidence élevée des anomalies autres que les décharges pointe-ondes 3 c/sec., en termes de la pathogénie de l'activité du petit-mal.

ZUSAMMENFASSUNG

1. Bei 100 Patienten mit klinischen Petit Mal Anfällen, welche mit "Spike-and-Wave"-Entladungen mit einer Frequenz von 3 Hz. verbunden waren, wurde das Auftreten von herdförmigen, lateralisierten und diffusen EEG-Veränderungen untersucht.

2. In 51 Fällen war die Ruheaktivität des EEGs normal. In 35 Fällen wurden herdförmige oder lateralisierte Veränderungen festgestellt, und in 14 Fällen war die Ruheaktivität in diffuser Weise abnorm.

3. Zweiundsechzig Patienten waren weiblichen Geschlechts. Das mittlere Alter des Auftretens der Petit Mal Anfälle war 7 Jahre; 19 Patienten hatten nahe Verwandte mit einer in Bezug auf Krampfanfälle positive Anamnese; 6 Patienten zeigten neurologische Symptome; 11 hatten einen niedrigen Intelligenzgrad. Bei 40 Patienten wiesen die Anfälle eine atypische Symptomatologie auf; 49 Patienten hatten nicht nur Petit Mal Anfälle, sondern litten auch unter anderen Anfallsarten. Mögliche ätiologische Faktoren konnten nur bei 5 Patienten anamnestisch eruiert werden.

4. Korrelationen wurden gefunden zwischen dem Vorhandensein von EEG-Veränderungen, welche verschieden waren von den üblichen "Spike-and-Wave"-Entladungen and dem Vorhandensein von entweder Schwachsinn oder positiven neurologischen Symptomen.

5. Die Frage wird besprochen, inwiefern Abnormalitäten anderer Natur als "Spike-and-Wave"-Entladungen mit einer Frequenz von 3 Hz. für die Genese der Petit Mal Aktivität eine Rolle spielen könnten.

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ANNOUNCEMENT

Fédération Mondiale de Neurologie
World Federation of Neurology

FORMATION OF COMMISSION OF NEUROCHEMISTRY

The Commission of Neurochemistry of the World Federation of Neurology met for the first time at the Institut Bunge in Antwerp, Belgium, on September 29 and 30, 1959. Dr. LUDO VAN BOGAERT, President of the Federation and Dr. CHARLES POSER, Medical Executive Officer, assisted at the meeting.

The following neurochemists had been invited and constituted the original Commission:

Dr. BAUER	Hamburg, Germany
Dr. BRANTE	Eskilstuna, Sweden
Dr. CUMINGS	London, England
Dr. EDGAR	Amsterdam, Netherlands
Dr. FOLCH-PI	Waverley, Mass., U.S.A.
Dr. KOREY	New York, U.S.A.
Dr. LOWENTHAL	Antwerp, Belgium
Dr. PEARSE	London, England
Dr. QUASTEL	Montreal, Canada
Dr. RICHTER	Cardiff, England
Dr. SVENNERHOLM	Göteborg, Sweden
Dr. TOURTELOTTE	Ann Arbor, Mich., U.S.A.

The Commission discussed the participation of neurochemists in the different international congresses. A permanent secretariat is to be established at the Institute Bunge, in Antwerp. Dr. A. LOWENTHAL was named Secretary of the Commission.

Plans were laid for holding a Symposium on Neurochemistry in Rome during the Congress of Neurology of 1961. The two major topics to be covered are: (1) Lipids, lipoproteins and their metabolism; (2) Disorders of myelin (not including disseminated sclerosis).

The Commission plans to establish a Registry of neurological material available for neurochemical investigation. In the near future, it is hoped that neurological associations, and neuropathological centers will be informed of the type of material wanted by the neurochemists and under what conditions this material is to be obtained and shipped. All requests and inquiries are to be addressed to the Secretary of the Commission who will see to it that the necessary contracts are made between physicians offering material and those requesting it for chemical study. It should be understood that although collaborative efforts are encouraged, each investigator retains full publication rights concerning the material he furnishes.

The Secretary of the Commission will endeavor to keep the various medical and scientific journals informed about the activities of the Commission and welcomes any suggestions from interested physicians.

LES RYTHMES RAPIDES DANS L'ÉLECTROENCÉPHALOGRAMME DE L'ENFANT

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(Received for publication: January 30, 1959)

De nombreuses recherches ont déjà été consacrées à l'électroencéphalographie du nourrisson et du jeune enfant. Les caractères physiologiques de l'électro-génèse cérébrale sont bien précisés et il en est de même des principales altérations qu'elle peut manifester. Certains types de grapho-éléments parfois présents dans l'électroencéphalogramme des jeunes sujets en cours de développement ont cependant reçu jusqu'ici peu d'attention. C'est en particulier le cas des grapho-éléments de fréquence supérieure à celle du rythme « alpha », qu'un certain nombre de caractères distinguent nettement des rythmes « bêta » physiologiques et que l'on peut classer sous le vocable de « rythmes rapides ».

Il convient tout d'abord de préciser et de définir soigneusement ce type de rythmes, les conditions d'enregistrements dans lesquelles ils ont été décelés, et les principaux grapho-éléments rapides « artefact » avec lesquels on se doit de ne pas les confondre.

MÉTHODES ET SUJETS

Nos recherches ont porté sur 15.000 EEG d'enfants de 15 jours à 15 ans et nous avons retenu comme rythmes rapides, des grapho-éléments de 14 à 30 c/sec. apparaissant avec un voltage supérieur à 20 μV. dans nos conditions standard d'enregistrement sur une ou plusieurs dérivations, ces sujets étant en état de veille.

Deux difficultés majeures se présentent quand il s'agit de repérer ce type de grapho-éléments: ne pas prendre des artefacts électromyographiques pour de tels rythmes et éliminer d'autre part les rythmes de fréquence élevée dûs à l'administration d'agents pharmacodynamiques générateurs de ce type d'activité, en particulier les barbituriques.

A priori, les décharges électromyographiques qui peuvent être enregistrées fortuitement au cours des examens EEG ne devraient pas pouvoir être confondues avec des éléments rapides d'origine cérébrale. Leur durée plus courte, les brusques variations de voltage qu'elles subissent dans de très courts laps de temps, leur siège (les artefacts électromyographiques occupent essentiellement les dérivations frontales et temporales), leur coexistence avec des mouvements musculaires macroscopiques, devraient permettre de les éliminer facilement. Dans la pratique, il n'en est pas toujours ainsi. Fréquemment en effet, le souci d'obtenir des tracés de meilleure qualité amène à introduire à l'entrée des chaînes d'amplification des filtres « passe-bas » qui, diminuant le voltage des fréquences électriques les plus élevées, confèrent alors aux décharges électromyographiques un aspect bien proche de celui des rythmes rapides vrais. En outre, les contractions musculaires des muscles de la nuque et des muscles temporaux peuvent être d'amplitude trop faible pour être décelées par l'œil de l'observateur et cependant donner naissance à une surcharge électromyographique. Ces considérations assez banales sont d'autant plus justifiées qu'il s'agit ici d'électroencéphalographie infantile.

Le deuxième « artefact » majeur à éliminer, consiste dans la surcharge des tracés par des grapho-éléments rapides d'origine barbiturique, qui présentent un aspect identique à celui des rythmes rapides spontanés. On ne peut éviter cette erreur que par un contrôle rigoureux de l'anamnèse et plus particulièrement de l'anamnèse thérapeutique.

Ces deux difficultés que nous venons d'exposer ont dicté notre conduite dans la discrimination des rythmes rapides spontanés et authentiques. Nous n'avons tenu pour tels que ceux apparaissant au cours d'un enregistrement effectué sur un sujet calme, détendu, éveillé, dont la tête est dans une position telle

qu'il ne saurait y avoir de contractions toniques des muscles de la nuque. En outre, nous avons rejeté les rythmes rapides n'apparaissant que dans les dérivations frontales et ceux observés lorsque des filtres « passe-bas » avaient été inclus dans les circuits d'amplification.

Quant aux éléments rapides barbituriques, leur existence nous a contraint à éliminer systématiquement tout tracé pour lequel nous ne disposions pas de renseignements suffisants sur les thérapeutiques appliquées ainsi que tous les sujets ayant reçu des barbituriques à quelque dose que ce soit depuis moins de quinze jours. Renchérissant enfin sur la rigueur de ces critères, nous n'avons pas hésité à écarter les cas seulement douteux et conservé exclusivement ceux où les activités rapides présentaient une constance, une amplitude et une morphologie enlevant toute hésitation sur leur réalité.

Dans ces conditions, il nous a été possible, en dépouillant 15.000 tracés représentant 9.070 enfants âgés de 15 jours à 15 ans, de relever dans 183 cas cliniques et dans 268 enregistrements la présence de ces grapho-éléments de fréquence supérieure à 13 c/sec. à morphologie assez typique lorsqu'on s'est entouré de précautions suffisantes (fig. 1). Cette proportion, pour faible qu'elle soit, n'est cependant pas insignifiante et justifie à notre avis qu'une étude d'ensemble soit consacrée à ces grapho-éléments. Ceci d'autant plus que la sévérité des critères utilisés permet d'affirmer que la proportion réelle des rythmes rapides doit être assez sensiblement supérieure.

Nous avons réparti les différents cas cliniques où se rencontraient des rythmes rapides en cinq catégories: les encéphalites et méningo-encéphalites en périodes d'état, les formes diverses de la comitialité (grand mal, petit mal, équivalents), les troubles du caractère, les retards psycho-moteurs et intellectuels, les affections diverses. Il convient de remarquer que les trois dernières subdivisions ne comprennent pas de sujets faisant des crises convulsives ou des équivalents comitiaux à la période où a été effectuée l'enregistrement.

Nous exposerons tout d'abord un certain nombre de résultats statistiques, puis nous envisagerons les catégories cliniques où il est possible de rencontrer fréquemment des rythmes rapides, les caractères particuliers qu'ils présentent et enfin leur apparition et leur évolution dans un certain nombre de cas cliniques.

I — DONNÉES GÉNÉRALES

A. *Répartition des rythmes rapides en fonction de l'âge des sujets.*

Si l'on considère une population électroencéphalographique quelconque dans un service d'électroencéphalographie donné, il est de constatation immédiate que le nombre des EEG enregistrés n'est pas égal pour les différents âges. Ce fait banal est encore beaucoup plus frappant quand on s'adresse à un centre d'électroencéphalographie infantile.

Nous considérerons ici la répartition des tracés et non des sujets en fonction de l'âge, car la plupart des enfants ont eu deux ou plusieurs tracés ayant pu être effectués à des intervalles de temps fort longs (jusqu'à 7 ou 8 ans).

La répartition des 15.000 tracés du service considéré en fonction de l'âge nous a donc fourni les résultats suivants:

	%
0 à 3 ans	34,2
3 à 6 ans	23,7
6 à 9 ans	17,7
9 à 12 ans	12,8
12 à 15 ans	11,5

Ce premier tableau permet de constater que plus de la moitié (57,6 pour cent) des tracés effectués dans le service concernait des enfants de moins de 6 ans. Si l'on enregistre maintenant la répartition par âge des tracés contenant des rythmes rapides, nous obtenons le tableau suivant:

		%
0 à 3 ans:	54 soit	20,1
3 à 6 ans:	36 soit	13,4
6 à 9 ans:	68 soit	25,4
9 à 12 ans:	67 soit	25
12 à 15 ans:	43 soit	16,1

Il ressort de ces données que la proportion est ici nettement inversée en faveur des tran-

ches d'âges supérieurs à 6 ans puisqu'elle représente 66,5 pour cent des tracés. Il nous apparaît qu'il existe là une corrélation significative et que ce type de grapho-éléments rapides est plus fréquemment rencontré chez les enfants les plus âgés. Ce fait n'a d'ailleurs à première vue rien de très surprenant puisque d'une façon générale, la fréquence des grapho-éléments tant normaux que pathologiques tend à croître dans le cours de l'électro-ontogénèse (Gibbs et Knott 1949).

B. *Répartition des rythmes rapides dans les différentes catégories cliniques considérées.*

Les différentes causes cliniques pour lesquelles sont pratiqués des examens électro-encéphalographiques chez l'enfant fournissent des proportions très variées de cas et d'enregistrements. Si nous nous rapportons aux cinq catégories cliniques précédemment citées, et aux 9.070 enfants qui ont été enregistrés, nous rencontrons la répartition suivante:

	suj.	%
Encéphalites et méningo-encéphalites	1.303 soit	14,3
Crises convulsives et formes diverses de la comitialité	3.753 ''	41,4
Troubles du caractère	1.297 ''	14,3
Retards psychomoteurs et intellectuels	1.229 ''	13,6
Divers	1.488 ''	16,4

En face de cette répartition; celle des sujets dont les tracés contiennent des rythmes rapides est toute différente:

	suj.	%
Encéphalites et méningo-encéphalites	24 soit	13,1
Crises convulsives et formes diverses de la comitialité	51 ''	27,9
Troubles du caractère	44 ''	24,0
Retards psychomoteurs et intellectuels	38 ''	20,8
Divers	26 ''	14,2

La considération de ces deux tableaux fait immédiatement ressortir un fait significatif, à savoir l'importante proportion d'enfants caractériels ou retardés présentant des rythmes rapides (44,8 pour cent à eux deux), par rapport à l'ensemble de la population électro-encéphalographique du service, qui comporte au contraire dans son ensemble un faible pourcentage de ce type de patients (seulement 27,5 pour cent pour l'ensemble de ces deux catégories réunies). Cette différence est encore plus significative si l'on se rapporte cette fois au pourcentage des tracés considérés comme anormaux.

Pour les 268 tracés contenant des rythmes rapides nous obtenons:

	tracés	%
Encéphalites et méningo-encéphalites	55 soit	20,5
Crises convulsives et formes diverses de la comitialité	92 ''	34,3
Troubles du caractère	49 ''	18,3
Retards psychomoteurs et intellectuels	45 ''	16,8
Divers	27 ''	10,1

Si nous envisageons maintenant les 11.290 tracés considérés comme anormaux et ne contenant pas de rythmes rapides, on voit aussitôt que la répartition est bien différente:

		%
Encéphalites et méningo-encéphalites	2867 soit	25,4
Crises convulsives et formes diverses de la comitialité	5329 ''	47,2
Troubles du caractère	531 ''	4,7
Retards psychomoteurs et intellectuels	836 ''	7,4
Divers	1727 ''	15,3

Ainsi les grapho-éléments de fréquence égale ou supérieure à 14 c/sec. se manifestent de préférence chez les enfants caractériels ou retardés. Il convient de rapprocher ce résultat des recherches effectuées tant chez l'enfant que chez l'adulte par un certain nombre d'auteurs. C'est ainsi que Hill (1944) a signalé des rythmes rapides chez des enfants présentant des troubles du comportement. De même Davis (1942) constate chez les schizophrènes une proportion relativement élevée de ces mêmes rythmes et Gastaut (1954) considère que chez l'adulte, une accélération du rythme de fond accompagne généralement les personnalités instables, hypersensitives, nerveuses, impulsives, sympathicotoniques ou d'une grande labilité affective. Il en est de même lorsqu'une médication appropriée crée une hyperexcitabilité intellectuelle et caractérielle. C'est ainsi que l'ingestion de doses convenables de D-lysergic-diéthylamide produit parallèlement une exagération des fonctions perceptives de l'activité, une instabilité affective, et une diminution des capacités d'attention, tous symptômes fréquemment rencontrés chez les enfants caractériels; en même temps qu'une accélération de l'alpha de 0,5 à 4 c/sec.

C. *Localisation des rythmes rapides en fonction de l'âge des sujets.*

Les éléments de 14 à 30 c/sec. que nous avons rencontrés dans 183 cas peuvent présenter des localisations différentes. Chez la grande majorité des sujets (136 cas, soit 74,3 pour cent du total), ils se décèlent seulement dans les dérivations les plus antérieures: frontales, temporales et pariétales. D'une façon plus générale on peut dire qu'ils ont une prédominance ou une localisation précentrale. Cependant pour le reste (47 cas, soit 25,7 pour cent du total), les grapho-éléments rapides sont localisés ou prédominent dans les dérivations post-centrales. Il est à remarquer que cette prédominance postérieure est surtout le fait des patients les plus jeunes. On en relève 27 cas sur 56 chez des enfants de moins de 6 ans, alors que pour 107 des 127 enfants de plus de 6 ans, la prédominance est antérieure. Par ailleurs on doit remarquer qu'il n'existe pas de différence dans la morphologie ou la fréquence de ces grapho-éléments en fonction de leur localisation.

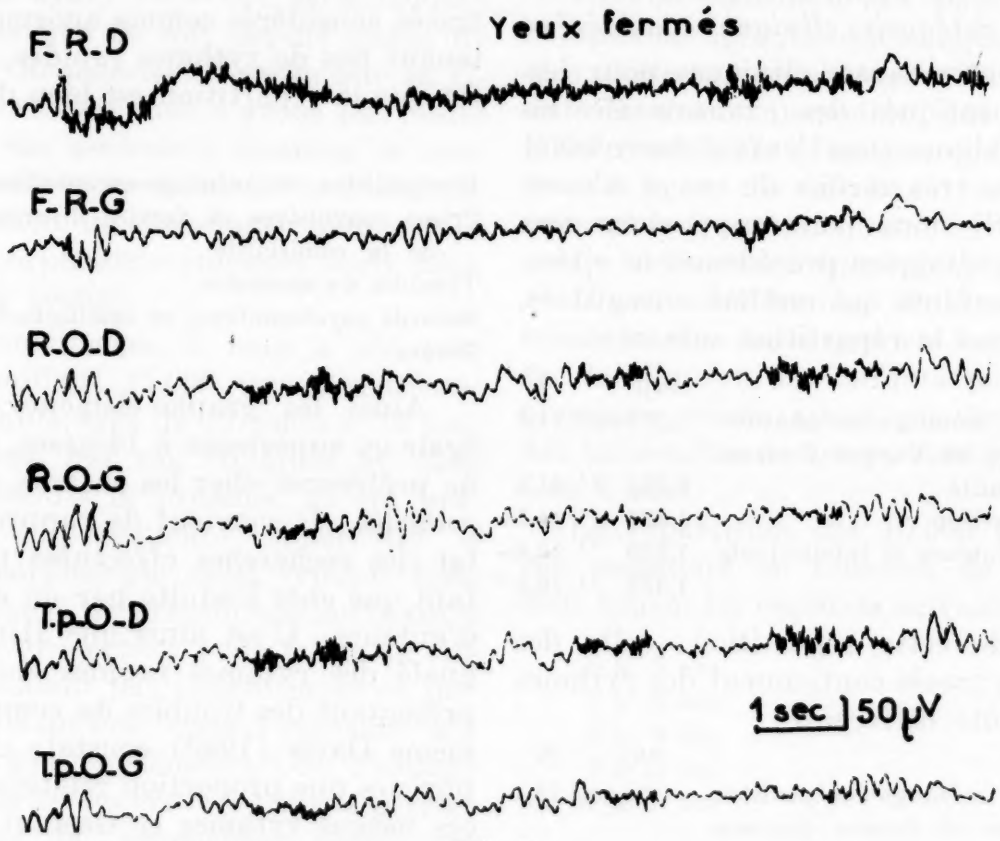


Fig. 1

Aspect général des rythmes rapides chez l'enfant. On notera les différences morphologiques très nettes de ceux-ci avec les artefacts électromyographiques observés sur les dérivations frontales.
Enfant de 9 ans ½ présentant des équivalents à type d'absence.

Quoi qu'il en soit, ce changement de la prédominance des rythmes rapides en fonction de l'âge doit être considéré comme l'indication d'une diversité possible de leur origine, ou peut-être simplement d'un déplacement progressif avec l'âge de ces grapho-éléments des régions post-centrales vers les régions précentrales comme il en est pour certains autres grapho-éléments pathologiques tels que certains foyers de pointes. Il faudrait, pour pouvoir trancher entre ces deux hypothèses, suivre un certain nombre de petits malades présentant des rythmes rapides, pendant un laps de temps suffisamment long, ce qu'il ne nous a pas été encore possible de faire.

II — PARTICULARITÉS ET ÉVOLUTION DES RYTHMES RAPIDES DANS DIFFÉRENTES AFFECTIONS

A. *Les rythmes rapides dans les encéphalites.*

Un des problèmes les plus intéressants que peuvent poser les rythmes de fréquence élevée dans l'EEG de l'enfant est celui de leur origine. Il n'est pas possible d'y répondre ac-

tuellement d'une façon certaine, mais l'étude suivie de certains cas de méningo-encéphalites (tuberculeuses en particulier) apporte des renseignements de grand intérêt.

C'est ainsi que nous avons eu l'occasion parmi les nombreux cas de méningo-encéphalites que nous avons enregistrés, d'en rencontrer un certain nombre dans les tracés électro-encéphalographiques desquels apparaissaient des rythmes de 14 à 30 c/sec. Il s'agit pour le plus grand nombre, de méningo-encéphalites tuberculeuses (14 cas sur un total de 24) ayant eu de nombreux enregistrements dans le cours de la maladie. Un certain nombre de traits communs rapprochent ces 14 cas. On est en présence pour tous de méningo-encéphalites tuberculeuses très graves où se trouvaient réunis à la fois des signes cliniques et des signes bioélectriques hautement pathologiques. Du point de vue EEG en particulier, on constatait dans les premiers enregistrements une désorganisation complète du rythme de fond remplacé par des ondes lentes et très lentes (moins de 3 c/sec.) généralisées et de haut voltage. Sous l'effet du traitement, ces éléments lents diminuaient peu à peu en nombre et en amplitude tandis que parallèlement les composants normales du rythme de fond réapparaissaient. Cependant, nous avons vu en outre se développer avec des délais extrêmement variables allant de 3 semaines à 2 ans, avec parfois un très long intervalle libre, pendant lequel le tracé paraît complètement normalisé, des rythmes rapides avec leur aspect bien caractéristique (voir fig. 2). Ils persistaient alors sans grand changement pendant des temps très longs pouvant atteindre et même dépasser deux années. Il est intéressant de noter que ces rythmes de fréquence supérieure à celle de l'alpha, ne se sont jamais accompagnés jusqu'à présent de manifestations cliniques pathologiques nettes. Il semble possible de les regarder comme une sorte de « cicatrice électrique » des atteintes histologiques définitives qu'à crées la méningo-encéphalite tuberculeuse. Par ailleurs, leur apparition progressive, leur aspect caractéristique très différent des éléments « bêta » physiologiques, l'âge des patients, l'absence de tout traitement barbiturique permet d'affirmer qu'il s'agit de grapho-éléments d'une individualité certaine et très nettement pathologique.

Du point de vue des mécanismes à leur origine, il est intéressant de les rapprocher des éléments de type voisin qui ont été rencontrés par Henry et Scoville (1952) dans des enregistrements électro-corticographiques fournis par des éléments isolés du cortex à la suite de lobotomies. Ces éléments en bouffées de 16 à 18 c/sec., que les auteurs ont dénommés: « suppression burst activity » remplaçaient les rythmes rapides habituels de l'imprégnation barbiturique, ne dépendaient pas de la profondeur de l'anesthésie et présentaient une longue persistance (un an au moins). Henry et Scoville les ont comparés aux grapho-éléments observés chez le Chat et succédant à des lésions de la base du diencéphale. Ils admettaient qu'ils étaient vraisemblablement dûs à une activité électrique corticale autogène indépendante de systèmes régulateurs thalamo-corticaux. Par ailleurs des études faites sur l'électro-corticogramme de régions cérébrales voisines de tumeurs, montrent que cette activité se rapproche de celle observée sur des lambeaux de cortex isolé d'animaux (Echlin, Arnett et Zoll 1952). Elle consiste en activités rapides (18 à 20 c/sec.) et de haut voltage. Ces résultats de Echlin et coll. se trouvent confirmés par ceux de Maleci et Shergna (1953), qui ont pu enregistrer une telle activité rapide sur le scalp de sujets atteints de tumeurs à développement lent. Ces auteurs suggéraient qu'elle serait dûe à un isolement partiel des masses cellulaires par les structures néoformées.

En conclusion, il ne nous apparaît pas impossible que les rythmes rapides observés chez des sujets ayant présenté des méningo-encéphalites tuberculeuses très graves soient dûs à l'activité quasi autonome de certaines régions du cortex ou tout au moins à des perturbations profondes dans les systèmes de régulations de l'électro-génèse.

B. *Les rythmes rapides dans les troubles du caractère.*

Les rythmes rapides que nous avons eu l'occasion (fig. 3) d'enregistrer chez 44 enfants présentant des troubles du caractère,

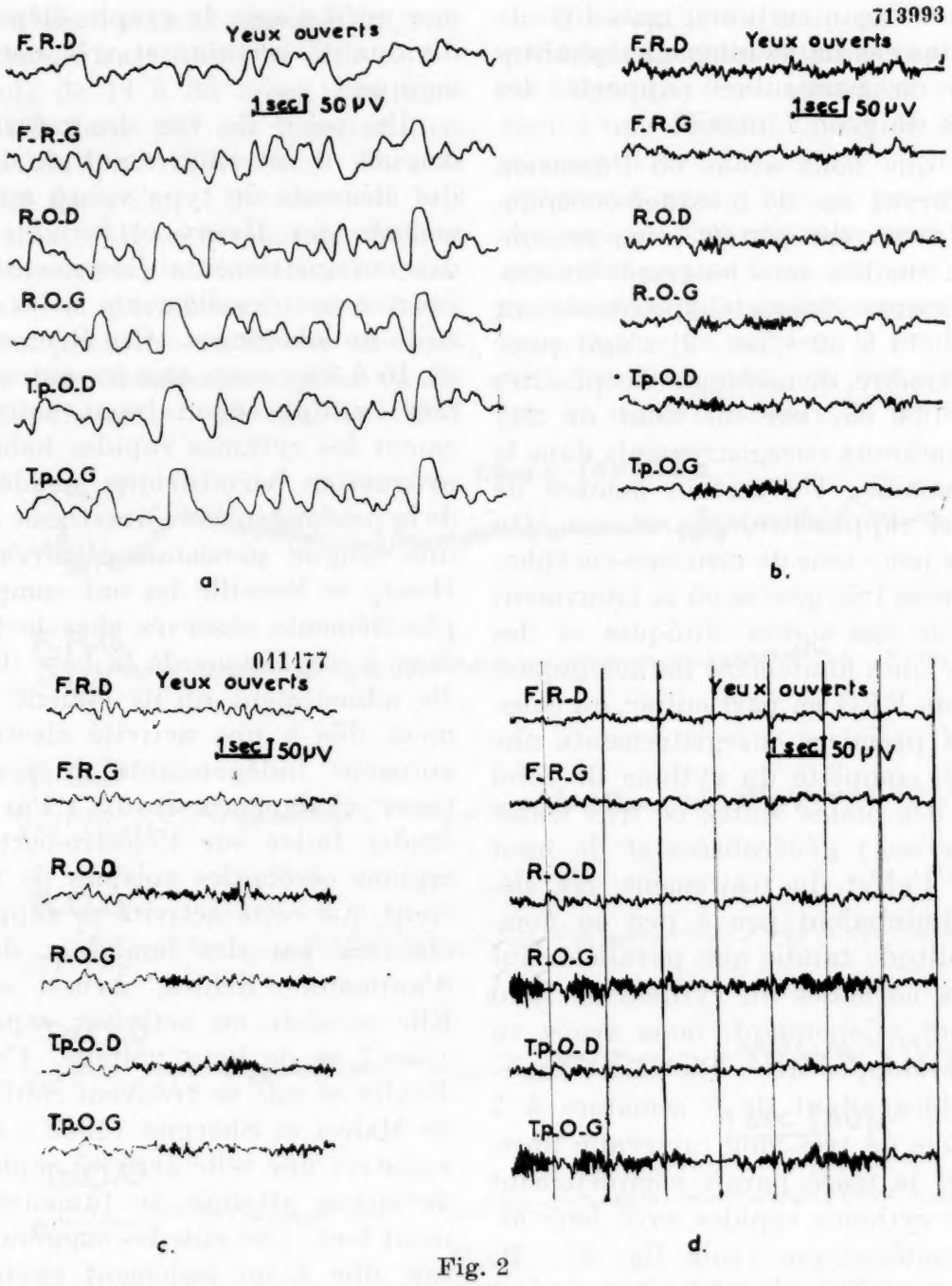
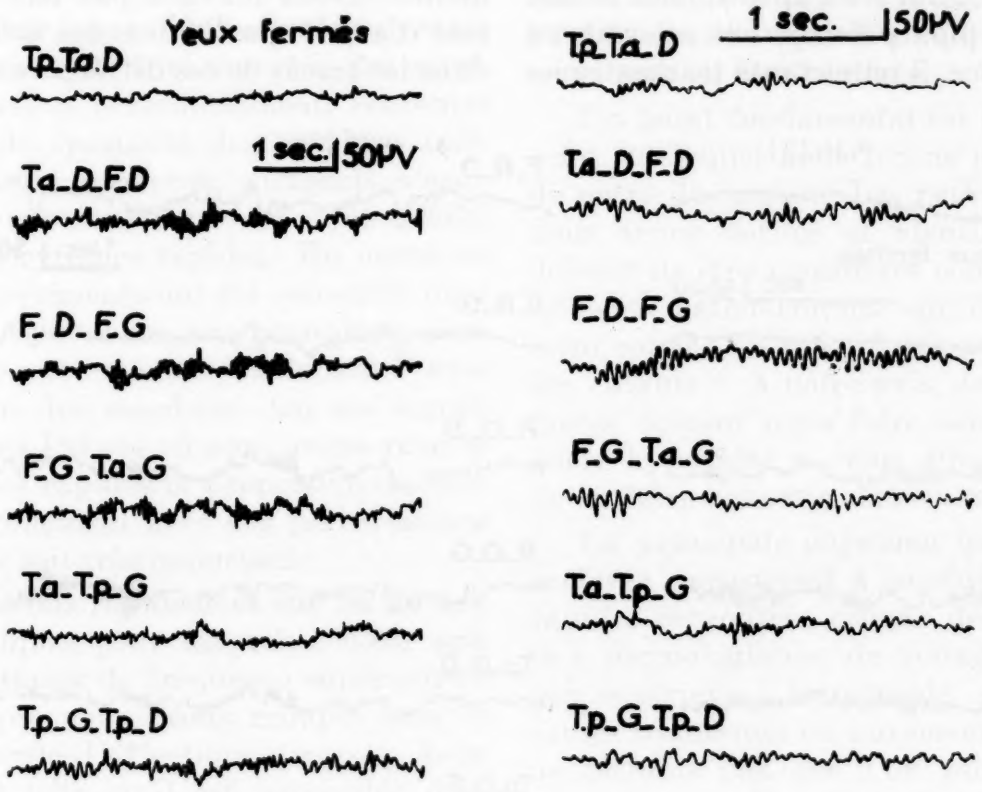


Fig. 2

Apparition progressive des rythmes rapides au cours d'une méningo-encéphalite tuberculeuse grave, chez une enfant de 22 mois.
a) Période d'état avant tout traitement. Troubles importants de la conscience.
b) 7 jours plus tard.
c) 1 mois plus tard.
d) 2 ans plus tard.

constituent un groupe très homogène. Il s'agit pour tous d'éléments compris entre 16 et 24 c/sec.; chez 37 d'entre eux ils présentaient une prédominance précentrale et chez 7 seulement une prédominance postcentrale. Enfin, dans 35 cas, ils étaient les seuls éléments pathologiques apparaissant spontanément dans le tracé ou au cours des épreuves d'activation habituelles: hyperpnée et stimulation lumineuse intermittente. Cette présence isolée des rythmes rapides au sein de tracés où le rythme de fond est par ailleurs normal, les distingue à notre avis de ceux observés dans les méningo-encéphalites où ils apparaissent au contraire pratiquement tous (21 fois sur 24) chez des patients ayant eu

ou ayant parfois encore de très importantes altérations. Il semble donc qu'il faille ici considérer les rythmes rapides comme une entité pathologique bien définie et justifiant le renouvellement des examens afin d'étudier leur évolution spontanée ou à la suite d'un traitement. Ils sont à ranger, pensons-nous, au nombre des troubles vrais de l'électrogénèse et ne doivent pas à notre avis être simplement assimilée à des rythmes « bêta » physiologiques de voltage élevé.



a. b.

Fig. 3
Rythmes rapides chez un enfant de 10 ans ½ sujet à des colères immotivées violentes et présentant une importante instabilité caractérielle.

C. *Les rythmes rapides dans la comitialité, les retards psycho-moteurs et diverses affections.*

Nous n'envisageons pas en détail les rythmes rapides qui peuvent être rencontrés dans des cas de comitialité avérée (grand mal, petit mal, équivalents). Il nous suffira de dire que dans cette catégorie d'affections, les rythmes rapides ne présentent rien qui permette de les distinguer de ceux rencontrés dans les catégories cliniques déjà étudiées; 42 fois sur 51, leur fréquence va de 16 à 24 c/sec.; 38 fois sur 51, ils prédominent dans les dérivations précentrales; dans 35 cas, ils coexistent avec d'autres altérations du tracé et dans 21 cas, on les trouve associés à une réaction fortement positive à la stimulation lumineuse intermittente. Ce fait est à rapprocher des considérations développées par Gastaut (1954), d'après lesquelles les tracés à rythme de fond rapide tendraient à manifester plus facilement que d'autres une réponse pathologique par recrutement sous l'effet de la photo-stimulation.

Une proportion relativement importante d'éléments de fréquence supérieure à 13 c/sec. a été également rencontrée dans les retards psychomoteurs et intellectuels. Ceux-ci constituent une proportion assez importante de la clientèle d'un laboratoire d'électroencéphalographie infantile, et sont bien entendu d'origines très diverses. Cette diversité se retrouve également dans les aspects électroencéphalographiques observés, allant de la normale à

l'hypsarythmie. Certains auteurs avaient eu l'occasion de rencontrer des rythmes rapides dans des arriérations avérées. C'est ainsi que Kreezer (1939) en avait déjà signalé dans des idioties phényl-pyruviques ainsi que chez des mongoliens. Dans les 38 cas que nous avons retenus, 31 consistaient en retards psychomoteurs importants sans étiologie bien manifeste et sans signes cliniques autres que le déficit intellectuel. Pour les 7 autres, nous avions des indications plus précises: on relevait un cas de mongolisme, 3 importants traumatismes obstétricaux, une embryopathie de la rubéole avec cécité, un retard très important, séquelle d'une encéphalite de la petite enfance d'origine inconnue, et enfin un myxoedème congénital traité depuis 5 ans à l'extrait thyroïdien. On peut d'ailleurs penser que dans ce dernier cas, les rythmes rapides sont peut-être dûs à la thérapeutique. On sait en effet que la thyroxine provoque une augmentation nette de la fréquence de l'alpha chez l'adulte et ceci parallèlement à l'augmentation du métabolisme basal (Jasper 1936; Lindsley 1937; Rubin 1937). Cet accroissement pourrait atteindre 1,7 c/sec. Cependant des auteurs qui ont particulièrement étudié les aspects électroencéphalographiques du myxoedème congénital, tels que Bertrand, Delay, Guillain (1938) et plus récemment Chaptal et Passouant (1956), n'ont jamais noté l'apparition de rythmes de fréquence supérieure à 13 c/sec. à la suite du traitement par l'hormone thyroïdienne. Nous n'avons pas par ailleurs constaté d'aspect particulier des éléments rapides dans les tracés de ces différents cas de retards, quelle que soit leur origine. Leur fréquence va de 15 à 24 c/sec., leur localisation est variable. Ils coïncident 16 fois avec des altérations manifestes, et 22 fois ils sont les seuls éléments non physiologiques du tracé. La figure 4 représente l'aspect typique des graphoéléments rapides tels qu'ils peuvent se rencontrer dans un retard psychomoteur. Il s'agit là d'un enfant de 2 ans et demi qui a subi un traumatisme obstétrical important. Il présentait au moment de l'examen une arriération considérable et en outre un syndrome moteur

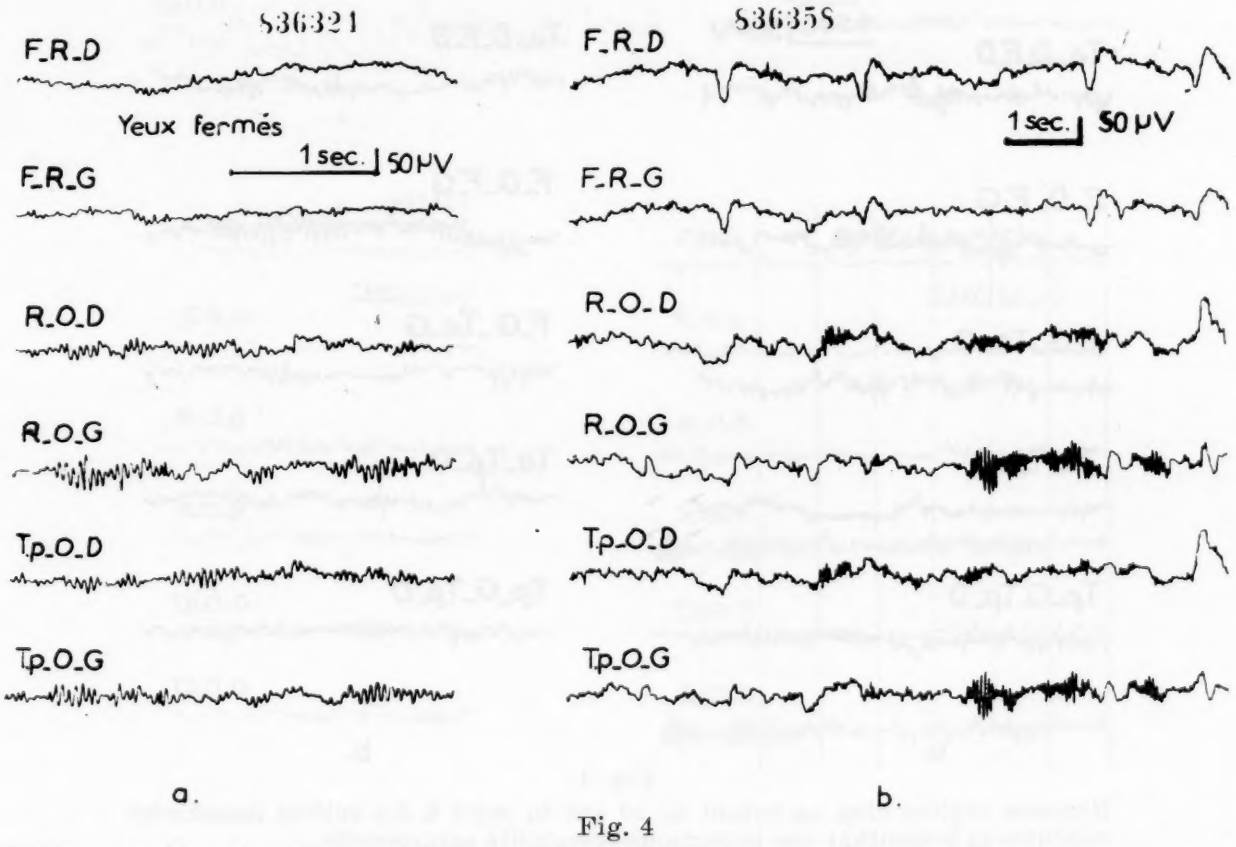


Fig. 4

Rythmes rapides chez une enfant de 2 ans ½ présentant un très important retard psychomoteur et un syndrome moteur rappelant une maladie de Little, auxquels s'associent des mouvements choréo-athétosiques.

rappelant celui de la maladie de Little, auquel s'associaient des mouvements athétosiques. Nous rapprocherons la coexistence de ces deux faits (retard et atteinte du système moteur pyramidal et extra-pyramidal) des constatations de Shiners, Krauss et Madigan (1950) qui, chez 28 enfants de 3 mois et demi à 10 ans, avaient trouvé des rythmes rapides de 18 à 20 c/sec. et de 30 à 50 μV. à prédominance précentrale, en même temps que des perturbations du système pyramidal et extra-pyramidal donnant une spasticité marquée des extrémités. Nous avons personnellement rencontré 2 autres cas de spasticité des membres inférieurs d'étiologie inconnue, auxquels s'associaient des crises convulsives et dont l'EEG présentait des rythmes rapides. En outre ces mêmes grapho-éléments ont été retrouvés dans une chorée de Sydenham, une hémiplégie cérébrale infantile, et une encéphalopathie avec hyperextension des membres. On ne saurait dire que sur les 183 cas où nous avons rencontré des rythmes rapides la proportion de ceux chez qui ils coïncident avec des perturbations de la motricité soit très importante.

Nous passerons rapidement sur les 26 derniers cas cliniques pour lesquels l'EEG présentait des rythmes de fréquence supérieure à 13 c/sec. et que nous avons groupés sous la rubrique générale d'affections diverses. Leur variété en est telle qu'il est impossible d'en tirer une conclusion quelconque ; on y rencontre en effet pêle-mêle quelques traumatismes crâniens, une xanthomatose cutanée, une maladie d'Apert-Crouzon, trois oedèmes papillaires isolés, une chorée de Sydenham, quatre cas d'hémiplégie cérébrale infantile, etc. On peut seulement noter que, dans tous ces cas, d'origines si diverses, l'aspect des éléments rapides reste très constant, que ceux allant de 16 à 24 c/sec. sont de beaucoup les plus nombreux et qu'on peut les rencontrer aussi bien isolés (13 fois) qu'associés à des altérations diverses.

DISCUSSION ET CONCLUSIONS

Au terme de ce travail, il nous appartient d'envisager l'ensemble des résultats que nous avons pu recueillir, discuter leur valeur et essayer de tirer quelques conclusions.

Nous pensons tout d'abord qu'il n'était pas inutile d'envisager chez l'enfant la signification des rythmes rapides, car ce type de grapho-éléments avait jusqu'à présent été fort peu étudié en EEG infantile, si l'on en excepte les données fournies par Lefebvre et Nekhorocheff (1951), ainsi que plus récemment par Garsche (1956). Par ailleurs, l'interprétation des tracés d'enfant n'ayant pas encore acquis la précision des tracés d'adulte, l'étude systématique d'un quelconque élément ne saurait en être négligée.

Un point fondamental est à établir et c'est celui sur lequel nous ferons porter l'essentiel de notre discussion. Les rythmes rapides que nous avons définis et identifiés comme tels doivent-ils être considérés comme des grapho-éléments pathologiques significatifs ou seulement comme un constituant normal de l'EEG des enfants ? A notre avis, des raisons importantes doivent nous faire souscrire à la première hypothèse et nous allons nous efforcer de les faire ressortir clairement.

La principale objection que l'on pourrait soulever consisterait à considérer les rythmes rapides rencontrés comme des éléments « bêta » physiologiques, de voltage seulement un peu supérieur à la normale, et ceci pour des causes techniques ou purement fortuites. Nous ne pensons pas que l'on puisse soutenir ce point de vue. En effet, *chez l'adulte*, ces grapho-éléments sont de très faible voltage, de fréquence pouvant aller jusqu'à 30 c/sec., et surtout réagissent très nettement à la fermeture des yeux qui les bloquent, ou aux mouvements des membres. Si nous reprenons ces différents points et que nous nous rapportions aux caractères décrits des rythmes rapides que nous avons rencontrés, nous voyons qu'ils n'ont pratiquement aucun caractère commun. En effet, Mundy-Castle (1951), qui a particulièrement étudié les rythmes « bêta » chez l'adulte, leur donne un voltage maximum de 20 μV. pour des distances inter-électrodes moyennes de 10 cm. en montages bipolaires. Dans ces conditions, on doit admettre que les grapho-éléments rapides retenus représenteraient au moins une très importante « exagération » des rythmes rapides physiologiques et cette seule augmentation est déjà en elle-

même, on doit en convenir, un fait pathologique.

Si nous envisageons maintenant une deuxième caractéristique des grapho-éléments que nous avons étudiés, c'est-à-dire leur fréquence, nous noterons qu'elle s'étend moins vers les fréquences relativement élevées que les rythmes « bêta » proprement dits. Ils ne dépassent jamais en effet 26 c/sec. contre 30 c/sec. Nous rapprocherons de cette donnée leur morphologie particulière. Les rythmes bêta physiologiques, et les auteurs insistent sur ce point, apparaissent comme une très fine activité assez continue ou irrégulièrement dispersée. Les rythmes rapides que nous avons étudiée accusent au contraire, aux mêmes vitesses de déroulement, un aspect « boudiné » assez typique (voir fig. 1), et que l'on retrouve facilement sur les illustrations.

Un troisième caractère différentiel est à notre avis fondamental, c'est la différence de réactivité des deux types d'éléments rapides que nous envisageons (bêta physiologique et bêta pathologique) : en effet, les éléments bêta physiologiques doivent être considérés, de l'avis à peu près unanime, comme une caractéristique du tracé d'éveil, l'indice de la mise en jeu de la formation réticulée activatrice et en conséquence sont bloqués par la fermeture des yeux ou tout au moins complètement masqués par l'activité alpha qui apparaît alors.

Or, et ceci est à notre point de vue fondamental, les rythmes rapides de l'enfant que nous avons étudiés ci-dessus, ne présentent aucune réactivité nette. On les voit apparaître *indifféremment* quand le patient a les yeux ouverts ou les yeux fermés. Peut-être dans ce dernier cas, sont-ils moins continus et leur aspect en « bouffées » moins caractérisé, mais en tous cas leur voltage ne présente pas de variations significatives.

Cette absence de réactivité vis-à-vis de la fermeture ou de l'ouverture des yeux se retrouve également en ce qui concerne la mise en jeu de la motricité volontaire. On sait que l'attention des électro-encéphalographistes a été récemment attirée par Mundy-Castle (1951), puis par Gastaut (1957), sur l'importante signification fonctionnelle des éléments bêta de la région prérolandique, surtout lorsqu'ils sont dits « dédoublés » (12 à 16 c/sec.). Dans ce cas en effet, ces éléments particuliers possèdent la faculté de n'apparaître que les yeux ouverts, et d'être bloqués par les incitations volontaires motrices (fermeture du poing par exemple). Autant de caractères qui font totalement défaut aux rythmes rapides que nous avons décrits et retenus.

Par ailleurs la localisation de ces éléments nous paraît moins stricte que celle des fréquences bêta physiologiques. Alors que ces derniers sont exclusivement précentraux, ceux que nous considérons présentent fréquemment une prédominance précentrale, mais aussi dans un nombre important de cas, ils sont à localisation exclusive ou à prédominance postérieure.

Nous citerons enfin un trait particulier aux rythmes rapides, qui nous est apparu seulement lorsque le nombre des cas envisagés a pris une certaine importance. Il s'agit de leur réactivité à l'hyperpnée. Dans 25 des cas, en effet, sur les 183 considérés, nous avons pu constater une nette augmentation de voltage moyen et du nombre des bouffées de ces rythmes rapides sous l'effet de l'hyperpnée. Il est intéressant par ailleurs de noter que cette réactivité particulière est essentiellement le fait d'éléments de fréquence relativement basse, très généralement inférieure à 18 c/sec. C'est en effet le cas 17 fois sur 25. Elle concerne particulièrement des sujets présentant des troubles de caractère (13 fois) et se répartit pour le reste sans différence significative entre les autres catégories cliniques. Il est possible que cette réactivité particulièrement nette à l'hyperpnée de certains éléments de la bande 14 à 18 c/sec. soit l'indication d'une différence dans les mécanismes à l'origine de cette activité. Mais il ne s'agit là bien entendu que d'une hypothèse, qui ne pourra se vérifier que lorsque le nombre des cas décelés se sera considérablement accru.

Il faut enfin remarquer que les rythmes rapides que nous avons étudiés ne sauraient en aucun cas être confondus avec les rythmes rapides du sommeil normal, ceux-ci en effet présentent une fréquence constante à 14 c/sec.

et surtout apparaissent chez l'enfant nettement endormi, alors que dans les 268 tracés que nous avons retenus, tous les enfants présentaient un niveau de vigilance normal.

L'ensemble des caractères que nous avons décrits aux rythmes rapides considérés, ainsi que leurs conditions d'apparition, nous amènent à penser que les rythmes rapides décrits par Garsche (1956) comme physiologiques ne sauraient être identifiés dans leur totalité à ceux que nous envisageons. Cet auteur admet en effet, dans l'article qu'il leur consacre, que les éléments bêta physiologiques de l'enfant ont une amplitude moyenne de 20,2 microvolts avec un écart moyen de plus ou moins 11 microvolts — qu'il n'existe pas de corrélation avec l'âge et en particulier qu'il peut en apparaître déjà, chez des enfants suffisamment jeunes pour présenter une activité électrique cérébrale à dominance delta. Ces grapho-éléments de fréquence supérieure à 13 c/sec., pourraient soit venir surcharger les rythmes dominants, soit venir interrompre leur cours; ils pourraient enfin être non influencés, activés ou bloqués par l'ouverture des yeux, l'hyperpnée et la stimulation lumineuse.

Si nous nous reportons aux critères d'identification que nous avons utilisés, nous voyons aussitôt que ceux-ci, très stricts, nous ont amené à écarter tous les rythmes rapides de voltage inférieur à 20 μV., donc la plus grande partie de ceux considérés comme physiologiques par Garsche. Par ailleurs, nous avons indiqué l'absence pratiquement complète de réactivité à l'ouverture des yeux, des grapho-éléments bêta que nous avons retenus, à l'inverse de ceux observés par ce dernier auteur. En outre, le fait que nous les ayons rencontrés chez des patients ayant tous présenté des manifestations pathologiques cliniques de types divers tend à prouver « a contrario » la réalité de leur signification pathologique.

Une dernière différence significative enfin : nous avons vu dans un certain nombre de cas, en particulier dans les méningo-encéphalites tuberculeuses, que ces éléments rapides *apparaissent* dans le cours de l'évolution de la maladie, principalement au moment de la guérison, ou tout au moins de l'amélioration clinique, et que l'on peut en suivre l'évolution sur un temps parfois long, mais pour finalement disparaître, signant ainsi leur caractère pathologique. Leur rétrocession est d'ailleurs dans la règle très lente, pouvant s'étendre sur plusieurs années. Au cours de celle-ci, leur topographie est susceptible de légères modifications (généralisation plus ou moins grande), mais leur fréquence et leur morphologie restent remarquablement constantes. Devant des caractères si nettement évolutifs, on ne peut imaginer que ces grapho-éléments d'une fréquence de 14 à 26 c/sec. soient un incident fortuit de l'électroencéphalogramme ou la simple manifestation d'un caractère physiologique rare de celui-ci. Leur signification anormale, pathologique, ne saurait faire de doute, et on doit en considérer la présence comme l'indication certaine de troubles de l'électrogénèse, dont la nature et la localisation restent à préciser. Quoi qu'il en soit, nous pensons, et ce sera notre conclusion, que les rythmes rapides de 14 à 26 c/sec. doivent être systématiquement recherchés dans les tracés électroencéphalographiques des enfants de tous âges, avec des précautions techniques suffisantes pour que leur identification soit certaine. Lorsqu'ils sont rencontrés, on doit les considérer comme pathologiques et suivre attentivement leur évolution dans les enregistrements ultérieurs, pour n'affirmer la normalisation du tracé que lorsqu'ils auront complètement disparu.

RÉSUMÉ

Les auteurs consacrent cet article aux rythmes rapides (de 14 à 30 c/sec.) présents dans les électroencéphalogrammes d'enfants de la naissance à 15 ans. Après avoir indiqué les conditions optimum d'enregistrement et les artefacts avec lesquels il convient de ne pas les confondre, ils étudient la proportion de ces grapho-éléments en fonction de l'âge et de diverses affections du système nerveux central (crises convulsives et formes diverses de la comitialité, encéphalites et méningo-encéphalites, troubles du caractère, retards psychomoteurs, etc....), ainsi que leur localisation. Ils insistent particulièrement sur l'apparition progressive des rythmes rapides au

cours des méningo-encéphalites tuberculeuses et y voient l'indication de séquelles électriques significatives.

L'étude de la réactivité des rythmes rapides envisagés dans cet article permet de les distinguer absolument des rythmes bêta physiologiques et des rythmes alpha rolandiques dédoublés. Ils doivent de ce fait être considérés comme des grapho-éléments pathologiques dont l'évolution doit être suivie attentivement, tandis que la normalisation du tracé ne doit être affirmée qu'après leur disparition.

SUMMARY

In this article, the authors study rapid rhythms (14 to 30 c/sec.) present in electroencephalograms of children up to 15 years of age. They outline the optimum recording conditions as well as the various artefacts brought about by recording itself and then proceed to study the relative proportion of the various elements of the records as a function of age and the different disorders of the central nervous system (convulsive seizures and different forms of epilepsy, encephalitis and meningo-encephalitis, maladjustment and psychomotor retardation, etc....), as well as their localization. They particularly stress the progressive onset of rapid rhythms during tubercular meningo-encephalitis and consider this as an indication that significant electrical sequels must be expected. The study of the reactivity of rapid rhythms considered in this article makes it possible differentiate them with certainty from physiological beta-rhythms and rolandic-rhythms. They must therefore be considered as pathological and their evolution should be close by followed and the tracing can only be considered as normalized once they have disappeared.

ZUSAMMENFASSUNG

Schnelle Rhythmen des Elektroenzephalogramms (14-30 Hz.), welche bei Kindern vom Neugeborenalter bis zu einem Alter von 15 Jahren angetroffen werden, wurden untersucht. Nachdem die optimalen Bedingungen für das Aufzeichnen dieser Rhythmen angegeben und die verschiedenen durch die Untersuchung selbst hervorgerufenen Störungen umrissen wurden, wird die relative Häufigkeit der verschiedenen Elemente in Funktion des Alters und verschiedene zentralnervöse Prozesse (Krampfanfälle und verschiedene Formen von Epilepsie, Enzephalitis and Meningoenzephalitis, Anpassungsstörungen und Verzögerungen der psychomotorischen Entwicklung u.s.w.) diskutiert und die Lokalisation dieser Rhythmen besprochen. Es wird speziell darauf hingewiesen, dass diese schnellen Rhythmen progressiv im Verlauf von tuberkulöser Meningoenzephalitis auftreten und ein Indiz für signifikante elektrographische Folgezustände darstellen.

Die Untersuchung der Reaktivität der schnellen Rhythmen ermöglicht es, sie in eindeutiger Weise von physiologischen Beta-Rhythmen und der Aktivität der Zentralregion zu unterscheiden. Dieser Aktivitätstypus muss daher als pathologisch betrachtet werden und seine Entwicklung sollte genau verfolgt werden. Das Hirnstrombild kann erst dann wieder als normal betrachtet werden, wenn diese schnelle Rhythmen verschwunden sind.

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ACTIVITÉS D'ORIGINE SOMESTHÉSIQUE ÉVOQUÉES AU NIVEAU DU CORTEX NON-SPÉCIFIQUE ET DU CENTRE MÉDIAN DU THALAMUS CHEZ LE SINGE ANESTHÉSIÉ AU CHLORALOSE[1]

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Amassian (1954), puis Albe-Fessard et Rougeul (1955, 1958), ont observé des réponses dans certaines régions du cortex associatif chez le chat anesthésié au chloralose à la suite de diverses stimulations du type somatique. Les derniers auteurs ont en outre établi le rôle de relais joué par le centre médian (CM) du thalamus dans ce système de projections convergentes. Il y avait lieu de se demander si un système projectif analogue, comprenant le même relais thalamique, existe aussi chez le singe.

TECHNIQUE

Nous avons utilisé 7 singes (4 *Macaca mulatta*, 1 *Cercocebus lunulatus*, 2 *Erythrocebus patas*). Leurs poids étaient compris entre 3,3 et 4,8 kg. Ces animaux ont été anesthésiés au chloralose intraveineux (7 à 8 cg. par kg.), l'anesthésie étant entretenue par des injections périodiques à faible dose. Dans la majorité des expériences, les animaux étaient en outre immobilisés au Flaxédil. Les stimulations (1 choc toutes les 3 sec.) étaient appliquées à l'aide d'électrodes piquées dans les membres. Les dérivations corticales ont toujours été effectuées entre une électrode active et une électrode indifférente. Les dérivations thalamiques étaient bipolaires entre deux électrodes concentriques dont les extrémités étaient décalées de 0,75 mm. La mise en place de ces électrodes fut repérée chez le *Macaca mulata* d'après l'atlas de Olszewski (1952). Un contrôle histologique ultérieur nous a permis en outre de vérifier dans chaque cas leur position.

[1] Recherches partiellement subventionnées par l'Air Research and Development Command, U.S.A.F., Contrat AF 61 (052) 103.

RÉSULTATS

A. *Divers types de réponses observables au niveau cortical lors de l'anesthésie au chloralose.*

Afin de pouvoir les comparer, nous avons, dans les figures 1, 2 et 3, groupé les divers types de réponses que l'on peut observer au niveau cortical après stimulation des membres. Nous avons d'abord cherché à montrer que chacune des réponses obtenues est bien individualisée et propre à une région donnée et qu'il n'y a pas à craindre que l'anesthésie employée détermine une extension des réponses primaires. Nous avons pour cela réuni dans un tableau les latences de ces réponses, mesurées systématiquement sur deux animaux. Nous les avons groupées en quatre types:

1° — Les potentiels primaires proprement dits, enregistrables dans le gyrus postcentral (C) ou aire SI; ils sont essentiellement contralatéraux et à courte latence. La distribution de ces réponses est, on le sait, somatotopique (Woolsey et Coll. 1942; Woolsey 1952).

2° — Nous avons retrouvé dans le gyrus précentral (PC) une autre représentation somatotopique des membres antérieurs et postérieurs (fig. 1 et 2). Les latences dans l'exemple choisi ici (fig. 1, 2 et tableau) sont légèrement plus élevées en moyenne que dans le gyrus postcentral. Ces faits concordent avec les résultats obtenus par Woolsey, Chang et Bard (1947), Malis, Pribram et Kruger (1953), Kruger (1956), Benjamin et Welker (1957).

3° — Nous avons observé en outre dans le gyrus temporal supérieur (TS) des réponses

bilatérales à courte latence ayant une certaine tendance somatotopique ; la représentation des pattes antérieures y est nettement plus large ; ces caractéristiques rattachent à l'aire SII ces réponses qui seraient probablement mieux visibles sur la lèvre antérieure de la scissure sylvienne (Woolsey 1943, 1944, 1946 ; Benjamin et Welker 1957). La grande amplitude des phénomènes observés semble cependant écarter la possibilité d'une simple diffusion électrique des réponses de la lèvre antérieure (voir aussi Oeconomos 1953).

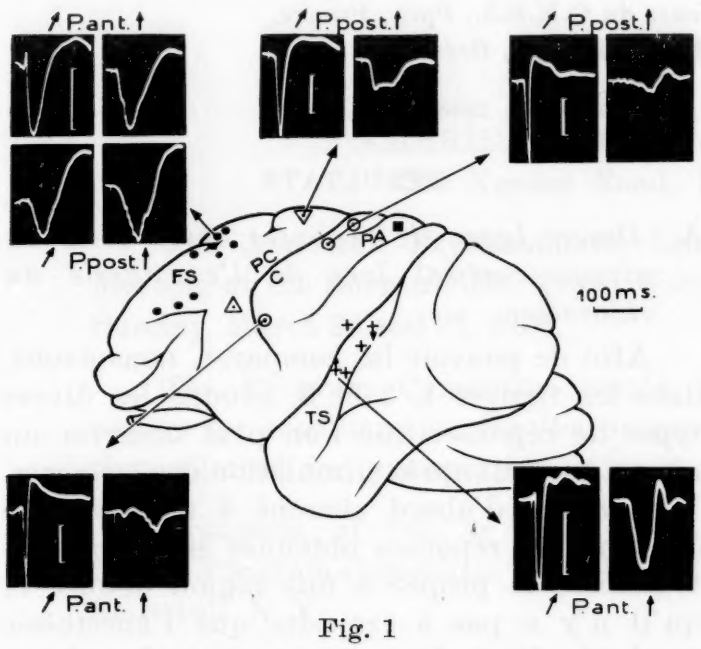

Fig. 1

Divers exemples de réponses obtenues sur le cortex gauche d'un macaque lors de la stimulation des membres antérieurs (P.ant.) ou postérieurs (P.post.), homo- (↑) ou contra-latéraux (→).
Cercles blancs. Potentiels évoqués primaires ; réponses à courte latence, uniquement contralatérales, dans le gyrus central (C).
Triangles. Potentiels évoqués dans le gyrus précentral (PC) ; seule, la réponse correspondant à la stimulation de la patte postérieure est représentée ici (voir aussi fig. 2).
Croix. Réponses bilatérales à courte latence dans le gyrus temporal supérieur (TS) :
flèche dirigée vers le bas : stimulation du membre postérieur ;
flèche dirigée vers le haut : stimulation du membre antérieur.
Carré noir. Aire associative pariétale (PA) ; on y recueille des potentiels évoqués en réponse à des stimulations provenant de diverses régions du corps (voir aussi fig. 3).
Points noirs. Dans le gyrus frontal supérieur (FS), des réponses apparaissent lors de la stimulation des quatre membres.

4° — En deux régions bien localisées enfin, nous avons observé des réponses dont la durée, la latence, les caractéristiques de convergence (sur lesquelles nous allons revenir), rappellent les caractères des réponses observées chez le chat au niveau du gyrus suprasylvien marginal antérieur et sigmoïde antérieur. Chez le singe, c'est dans le gyrus frontal antérieur (FS) et la partie postérieure du gyrus postcentral, appelée souvent aire 5 ou aire pariétale associative (PA) (voir fig. 1)

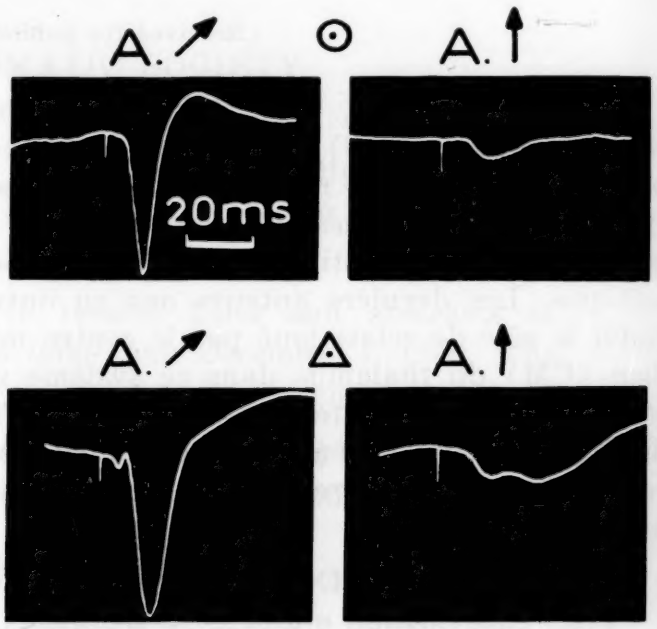

Fig. 2

Réponses observées chez un autre macaque dans les gyrus central et précentral (mêmes conventions de symboles que dans la fig. 1). Stimulation d'une patte antérieure (A) contra- ou homolatérale.

que l'on peut observer ces réponses qui n'avaient pas été décrites jusqu'à présent. Nous allons maintenant en étudier les caractéristiques.

B. *Caractéristiques des réponses évoquées dans le gyrus frontal antérieur et l'aire pariétale associative par la stimulation somesthésique.*

1° — Dans les deux régions du *gyrus frontal antérieur,* repérées par des points noirs sur la figure 1, mais plus particulièrement au niveau le plus proche de l'apex, nous avons obtenu des activités évoquées en appliquant la stimulation à l'un quelconque des quatre membres (voir fig. 1, 3, 5, 6). Les latences minima observées chez deux animaux différents au niveau du gyrus frontal supérieur sont données dans le tableau. On re-

COMPARAISON ENTRE LES LATENCES DES RÉPONSES RECUEILLIES EN DIVERSES RÉGIONS

	Dérivation	Stimulation			
		membre antérieur		membre postérieur	
		contra-	homo-	contra-	homo-
ERYTHROCEBUS PATAS		msec.	msec.	msec.	msec.
	Aire primaire SI				
Stimulation de l'extrémité des membres	région membre antérieur	9,3*(0,36)*	—	—	—
	" " postérieur	—	—	13,1*(0,45)*	—
Moyenne de 20 mesures	*Gyrus frontal*				
	partie supérieure	14,8*(0,96)*	18,3*(0,95)*	17,8*(0,44)*	20,9*(1,49)*
Température centrale: 38°	" inférieure	16,0*(0,64)*	16,5*(1,23)*	19,5*(0,79)*	22,0*(1,47)*
	Aire pariétale associative	13,9*(0,54)*	18,4*(1,00)*	23,0*(1,35)*	34,8*(3,75)*
MACACA MULATTA					
	Aire primaire SI				
Stimulation du bras et de la cuisse	région membre antérieur	8	—	—	—
	" " postérieur	—	—	12	—
Moyenne de 6 mesures	*Aire motrice*				
	région membre antérieur	10	—	—	—
Température centrale: 37°5	" " postérieur	—	—	15	—
	Gyrus frontal				
	partie supérieure	12	13	16	16
	" inférieure	13	13	20	20
	Aire pariétale associative	9	11	13	13

Les latences sont déterminées par l'intervalle séparant le stimulus du début de la réponse.
Les chiffres entre parenthèses représentent l'écart-type.

marquera qu'elles sont plus longues que les latences des autres types de réponse.

Ces activités essentiellement positives sont caractérisées en outre par leurs longues durées (50 à 80 msec. alors que, dans les mêmes conditions, le potentiel primaire dure de 10 à 20 msec.) Dans une même région corticale, des messages afférents de plusieurs origines sont capables de provoquer une réponse. Nous avons en effet pu observer, par l'utilisation de doubles chocs hétérogènes, des occlusions entre les diverses activités provoquées. Ces occlusions sont encore visibles après plusieurs centaines de msec.; elles ont pu être observées entre messages provenant des divers membres pris deux à deux; la figure 4 en donne deux exemples.

L'ensemble de ces caractéristiques rapproche les réponses associatives que nous décrivons chez le singe de celles que nous avons observées chez le chat. Signalons cependant

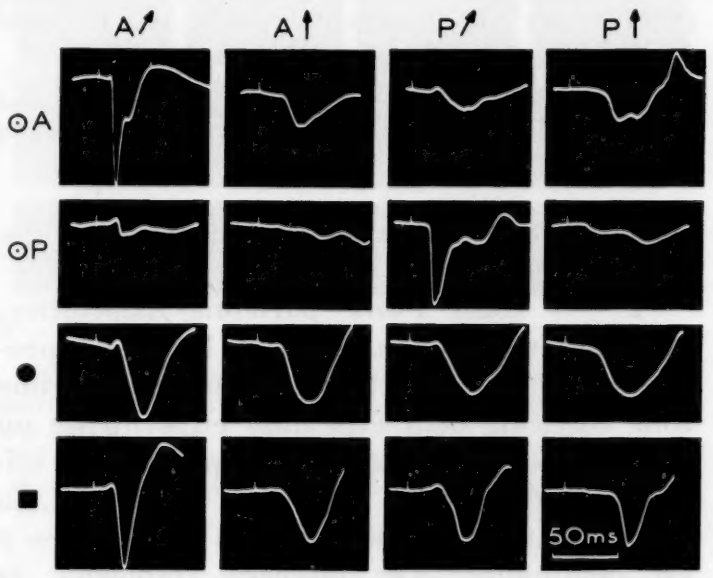

Fig. 3

Erythrocebus patas. Réponses évoquées lors de la stimulation des membres antérieurs (A) ou postérieurs (P), contra- ou homo-latéraux.
Cercles blancs. Régions primaires de la patte antérieure (A) ou postérieure (P).
Cercle noir. Gyrus frontal.
Carré noir. Aire pariétale associative.

deux points qui les différencient de celles observées dans le gyrus suprasylvien du chat :

a) Les réponses maximales observées n'apparaissent pas ici dans une zone extrêmement étroite ; elles occupent des zones corticales relativement plus étendues, de plusieurs mm.², au lieu de 1 à 2 mm.² sur le gyrus suprasylvien du chat.

b) Les occlusions observées entre afférences hétérogènes ne sont pas toujours totales, mais souvent partielles, montrant que nous avons probablement affaire à des zones

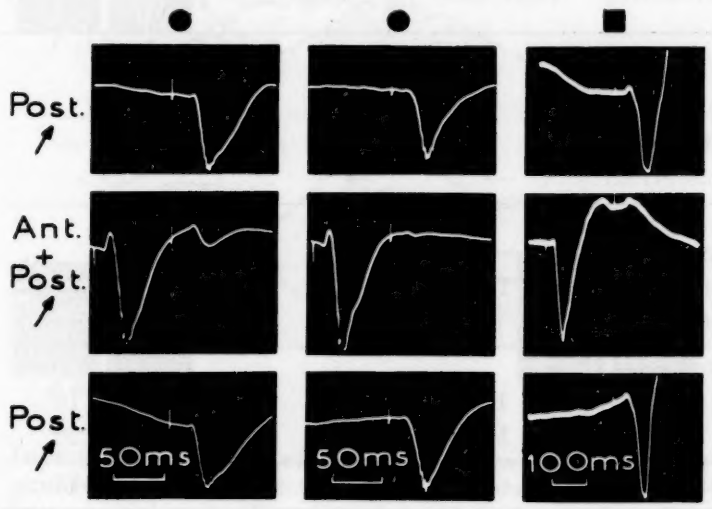

Fig. 4

Trois exemples d'interactions entre réponses d'origines différentes (stimulation de la patte postérieure précédée par une stimulation portée sur la patte antérieure).
Les deux colonnes surmontées d'un point noir correspondent à deux régions différentes du gyrus frontal antérieur. La troisième colonne correspond à l'aire pariétale associative.

chevauchantes de projection, plutôt qu'à une aire de convergence parfaite.

2° — Dans l'*aire pariétale associative,* immédiatement en arrière de l'aire de projection primaire de la patte postérieure, une zone corticale peut être mise en évidence où l'on peut observer aussi des réponses à la stimulation des quatre membres ; cependant, la représentation des deux pattes antérieures y est dominante. Les latences (tableau), la durée de ces réponses, sont comparables à celles des réponses de la région frontale (fig. 3 et 6). Des occlusions totales ou partielles se produisant entre afférences de diverses origines ont pu en outre être observées dans cette région (voir fig. 4).

3° — *L'individualité de ces deux types de réponses* est prouvée par leur localisation étroite bien distincte de celle des réponses primaires observées dans les gyrus central et postcentral. On met bien en évidence ce caractère par les discontinuités que l'on observe dans la localisation, la durée, la latence des divers types de réponses lorsqu'on déplace progressivement une électrode dérivatrice sur le

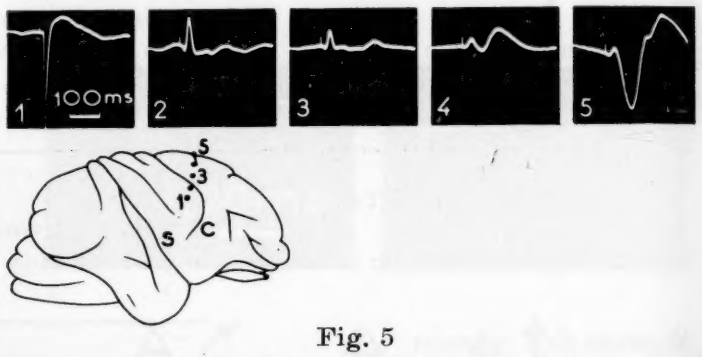

Fig. 5

Réponses à la stimulation de la patte antérieure contra-latérale, observées en 5 points alignés, séparés approximativement de 2 mm. Observer la discontinuité lorsqu'on passe de l'aire primaire (1) à l'aire frontale associative (5).
C, scissure centrale ; S, scissure sylvienne.

trajet passant par l'aire primaire de représentation de la patte antérieure (fig. 5) ou de la patte postérieure (fig. 6) et allant vers l'aire frontale. Outre les régions de silence séparant les réponses, la figure 6 montre combien les propriétés de convergence différencient les aires associatives de l'aire primaire.

C. *Activités spontanées et activités évoquées au niveau du gyrus frontal.*

Au cours de quatre expériences, nous avons enregistré sur scripteur les activités spontanées et les activités provoquées dans la région frontale et dans certaines régions du thalamus pendant la stimulation d'un membre. Nous avons observé les faits suivants :

a) L'activité spontanée est profondément modifiée (accrue en amplitude) dans les régions associatives et au niveau du CM, mais aussi au niveau du cortex primaire lorsque nous injectons du chloralose à un animal sur le point de s'éveiller (fig. 7).

b) En comparant les activités spontanées et les activités évoquées bilatérales de la région limitant postérieurement le gyrus frontal, on constate que les zones où sont obtenues les

activités évoquées les plus amples se trouvent dans une région qui présente une activité spontanée intense (fig. 8). Mais on observe en outre que les activités spontanées de grande amplitude occupent une large région du lobe frontal, beaucoup plus large que celle où nous provoquons des activités évoquées à caractéristiques convergentes. Les activités évoquées sont maximales à la limite postérieure de l'aire active spontanément; c'est pourquoi elles apparaissent dans ces régions avec l'activité spontanée. Ces faits expliquent ainsi pourquoi fréquemment les activités évoquées sont difficiles à observer chez les animaux en anesthésie peu profonde, l'activité spontanée intense les rendant fluctuantes.

D. *Relais thalamiques vers les aires associatives.*

Seuls les *Macaca mulatta* furent utilisés pour les recherches nécessitant des dérivations stéréotaxiques. Le nombre restreint des animaux dont nous avons pu disposer ne nous a permis d'effectuer jusqu'ici que des expériences préliminaires. Nous nous sommes limités à l'identification des relais thalamiques ou subthalamiques relatifs aux projections de la région frontale.

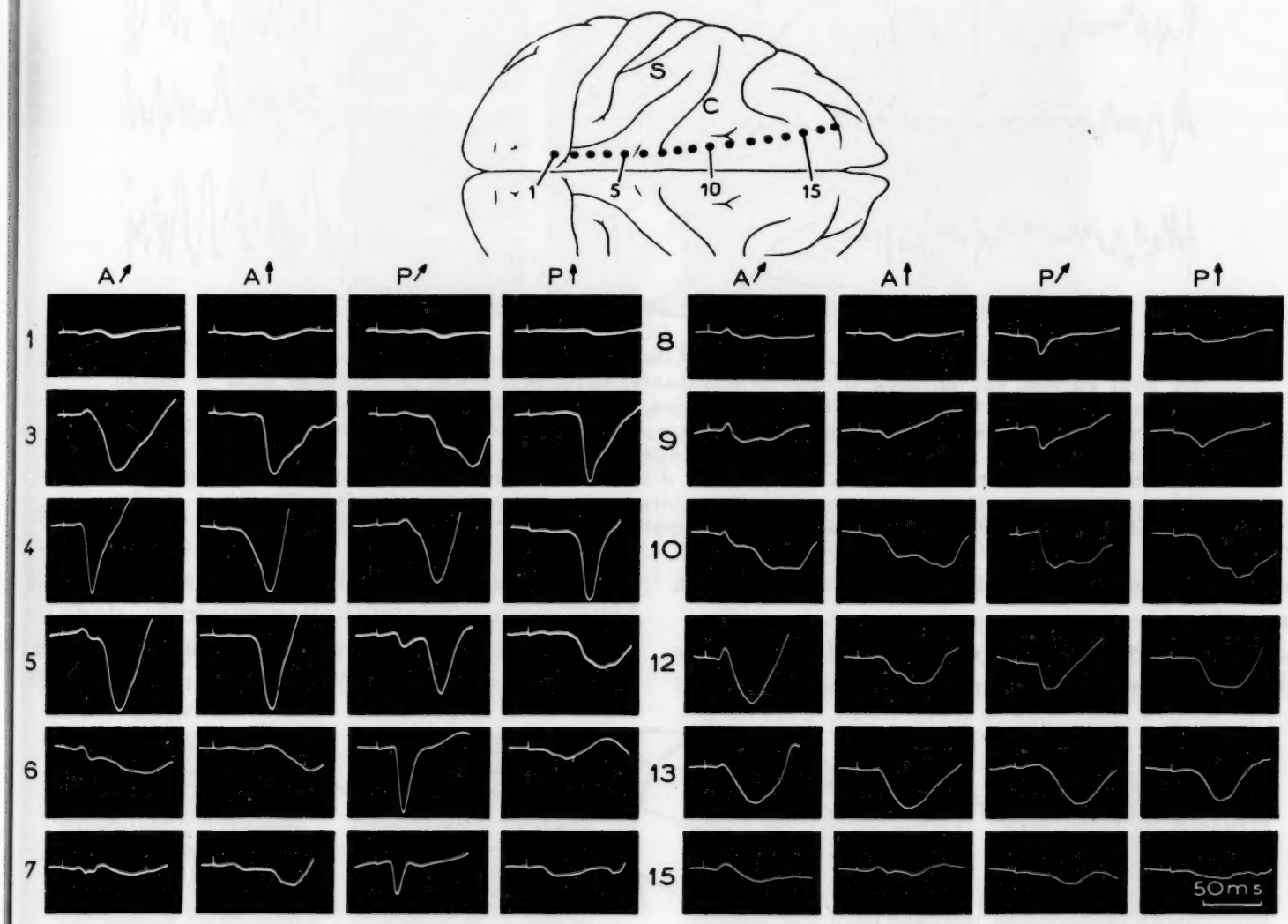

Fig. 6

Réponses observées en une série de points alignés, régulièrement espacés, lors de la stimulation des quatre membres. On remarquera les modifications significatives de la réponse lors du passage par l'aire pariétale associative (maximum en 4), par l'aire primaire de la patte antérieure (6), par l'aire frontale associative (10 à 13). Les points non représentés étaient silencieux (2, 14, 16, 17) ou correspondaient à des réponses identiques à celles des points voisins (11 analogue à 12).

1° — Conduits par les résultats de notre précédent travail chez le chat, nous avons cherché des régions de relais présentant des propriétés de convergence à deux niveaux sous-corticaux, soit le centre médian et la zona incerta.

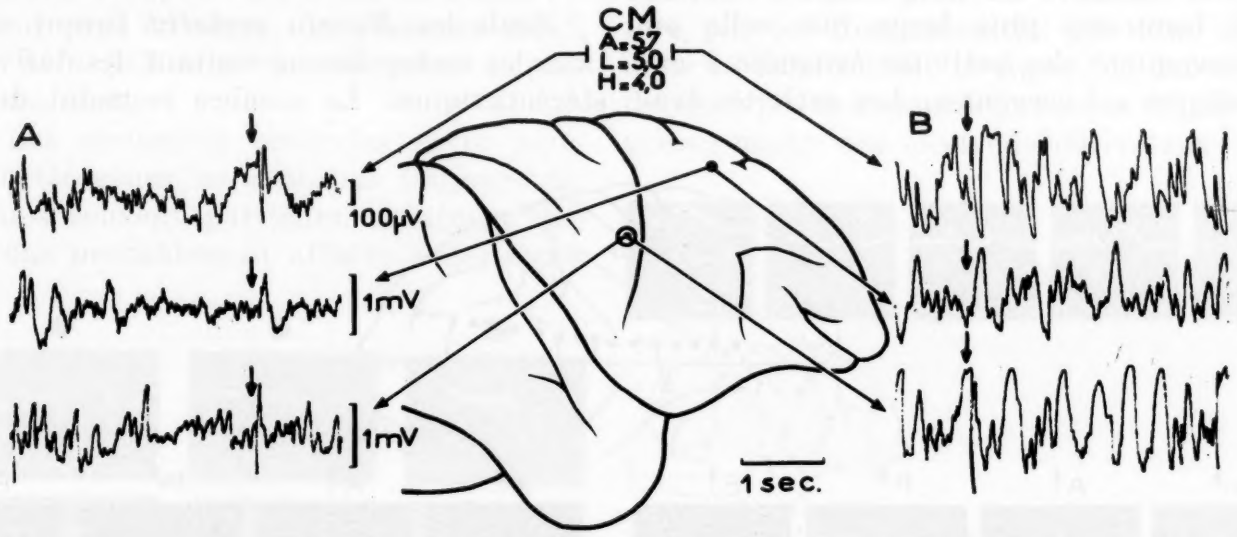

Fig. 7

De haut en bas, sur un fond d'activité spontanée, enregistrements de réponses dans le noyau centre médian du thalamus (CM; coordonnées de Horsley-Clarke: A, L, H), sur le gyrus frontal supérieur, ici en une région peu active, sur le cortex somesthésique primaire, lors de la stimulation de la patte antérieure contra-latérale. En A, l'animal est très légèrement anesthésié au chloralose. En B, l'injection d'une dose supplémentaire d'anesthésique vient d'être pratiquée. On remarquera l'accroissement concomitant des activités évoquées et des activités spontanées (les deux tracés ne sont séparés que par la durée de l'injection).

a) *Au niveau du centre médian,* comme French, Verzeano et Magoun (1953) l'avaient déjà montré, des stimulations somatiques diversement situées provoquent chez le singe des réponses dans une même région de ce noyau; ainsi, des réponses y sont observées lors de la stimulation des quatre membres (voir tracés de la fig. 9 et noter la position de l'électrode correspondante). L'activité spontanée importante que nous avons signalée plus haut comme pouvant être observée dans le CM pour certaines conditions d'anesthésie légère (fig. 8) rend souvent fluctuantes les réponses évoquées thalamiques, de même qu'elle rendait fluctuante celles des aires corticales associatives. Nous avons pu à ce niveau thala-

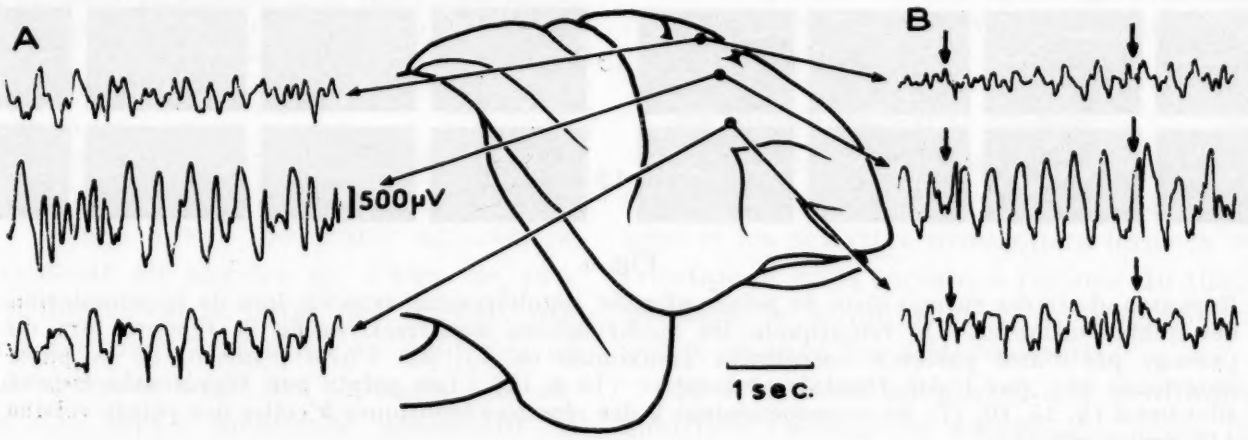

Fig. 8

Dérivations simultanées en trois points du gyrus frontal supérieur: A, activités spontanées; B, activités spontanées avec deux stimulations (flèches) de la patte antérieure contralatérale. On remarquera que la région spontanément la plus active est celle où les activités évoquées sont les plus amples.

mique observer des occlusions entre les afférences (provenant des divers membres) qui convergent sur ce noyau.

b) Au niveau de la zona incerta, nous avons pu aussi (fig. 10), comme nous l'avions montré chez le chat, mettre en évidence des activités convergentes (Oswaldo-Cruz et coll. 1956).

2° — Nous avons pratiqué la stimulation du centre médian et recherché si des réponses apparaissent sur le cortex. Tel est bien le cas en effet pour la région frontale que nous avons seule étudiée en détail. Une stimulation ménagée fait apparaître des réponses là où nous trouvions des activités évoquées à la suite des stimulation périphériques (fig. 11). Nous n'avons pu jusqu'à présent étudier les relations du subthalamus avec ces régions.

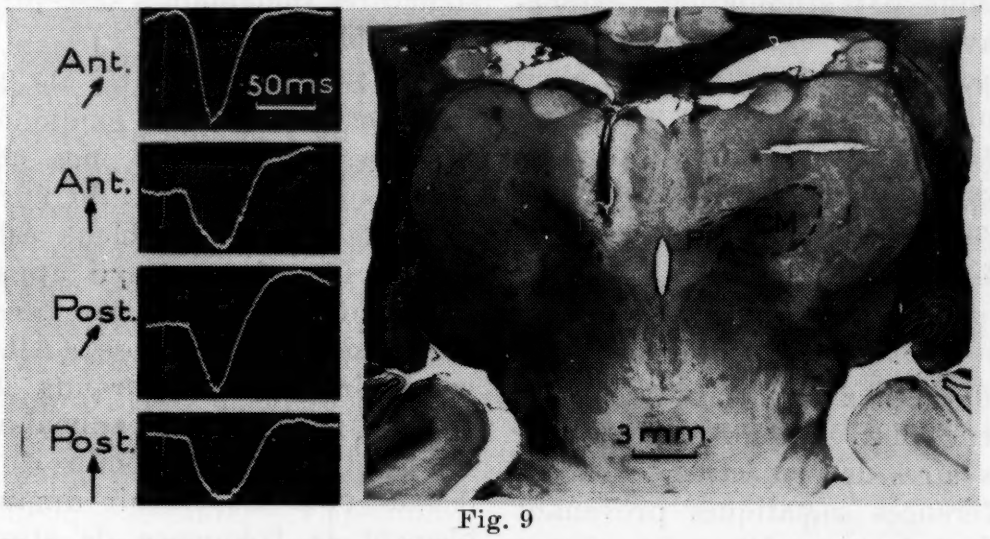

Fig. 9

Macaca mulatta. A gauche, réponses recueillies dans le centre médian lors de la stimulation des quatre membres. A droite, photographie d'une section frontale (A = 5,7) montrant dans sa moitié gauche la trace de l'électrode utilisée pour les enregistrements. Sur la moitié droite, ont été tracées les limites du centre médian (CM) et du noyau parafascicularis (Pf).

3° — Nous avons ensuite procédé pour ces diverses dérivations à une étude comparée des latences, cherchant à montrer que la latence périphérie-cortex était sensiblement égale à la

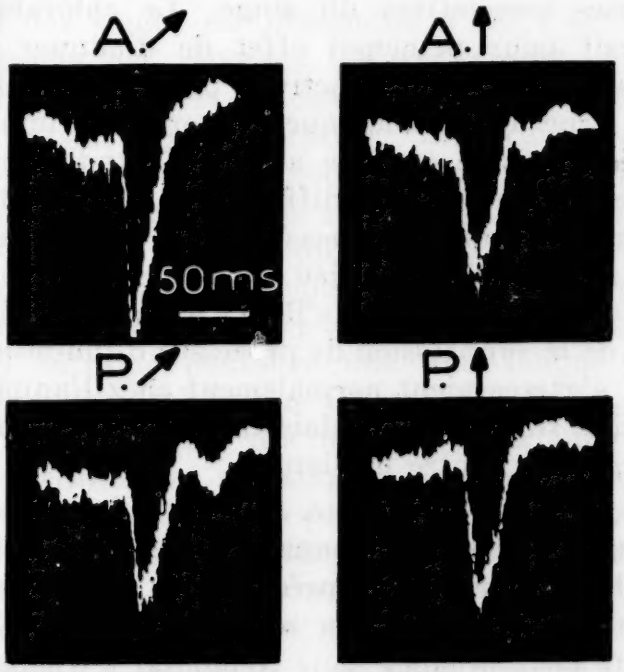

Fig. 10

Macaca mulatta. Réponses recueillies au niveau de la zona incerta lors de la stimulation des quatre membres.

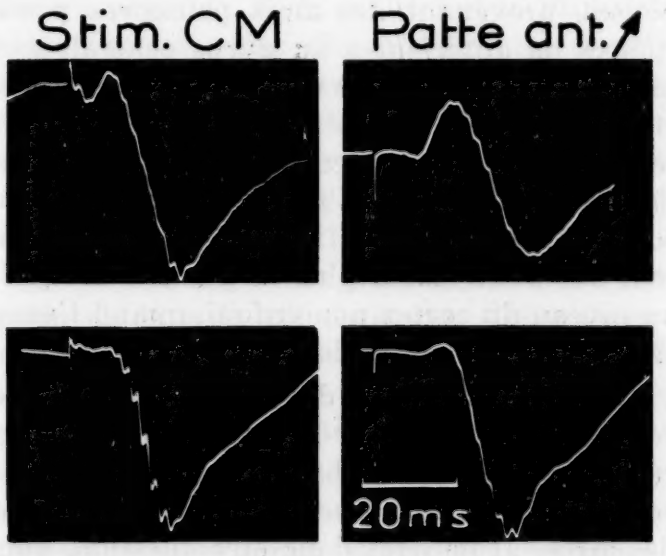

Fig. 11

Comparaison, pour deux points du gyrus frontal antérieur, des réponses observées lors de la stimulation, soit du centre médian, soit de la patte antérieure contra-latérale.

somme des latences partielles périphérie-centre médian + centre médian-cortex. Cette somme, dans les quelques expériences où des mesures précises ont pu être faites, s'est malheureusement toujours montrée supérieure à la latence obtenue par stimulation périphérique. Nous avons par exemple trouvé 24 msec. pour la somme des deux latences alors que nous obtenions 20 msec. pour la latence directe. La latence CM-cortex, de l'ordre de 8 à 10 msec., est toujours assez longue, comparée à la latence observée dans les mêmes conditions chez le chat.

DISCUSSION

Au cours de ce travail, nous avons pu mettre en évidence chez le singe anesthésié au chloralose deux aires de projection, où aboutissent des afférences somatiques provenant de diverses régions du corps, l'une se trouvant au niveau de la partie postérieure du gyrus frontal, l'autre dans l'aire pariétale associative. Ces aires sont sans doute les homologues des zones corticales que nous avons décrites chez le chat dans les mêmes conditions d'anesthésie, et au niveau desquelles Buser et Borenstein (1957) ont trouvé des réponses de faible amplitude chez le chat éveillé immobilisé au Flaxédil. A titre comparatif, nous avons en outre dérivé les réponses des aires primaires. Les caractéristiques de ces réponses, provenant des aires primaires postérieures ou antérieures au gyrus central, sont sensiblement les mêmes que celles des réponses étudiées sous Nembutal par de nombreux auteurs, au moins pour leurs formes et leur localisation (leurs latences semblent toutefois plus courtes). Les seules différences observées portent sur l'extension, plus large, de l'aire SII au niveau du cortex non enfoui, quand l'anesthésique est le chloralose.

Les diverses aires de projection se différencient nettement par les caractéristiques des réponses qui y sont observées et par les discontinuités de ces caractéristiques aux limites des aires. Il ne peut donc être question, pour expliquer l'apparition des réponses frontales et pariétales, d'invoquer une extension des réponses primaires qui serait due à l'anesthésique employé. Il s'agit bien de la mise en évidence de projections d'un nouveau type, révélées par l'usage du chloralose.

Nous discuterons tout d'abord de cette action élective du chloralose sur les systèmes convergents, puis nous examinerons le rôle des structures thalamiques susceptibles de relayer ce type d'afférences.

a) Les particularités de l'anesthésie au chloralose ne sont pas expliquées par nos expériences. Cependant, nos observations récentes sur les réponses du noyau caudé chez le chat curarisé semblent éclaircir le problème. Les réponses qui apparaissent régulièrement dans cette structure chez le chat anesthésié au chloralose (Albe-Fessard, Oswaldo-Cruz, Rocha-Miranda 1958) peuvent apparaître aussi chez l'animal opéré sous anesthésie à l'éther et immobilisé au Flaxédil, mais il faut pour les obtenir diminuer considérablement la fréquence de stimulation (nous avons retrouvé le même phénomène avec le centre médian). Chez le chat curarisé non anesthésié, les stimuli doivent être espacés d'environ 20 sec. au moins, alors que le chat sous chloralose supporte une stimulation toutes les 3 sec. Le nombre insuffisant d'animaux ne nous a pas permis de procéder ici à la même expérience mais il est raisonnable d'invoquer un phénomène analogue pour les réponses associatives du singe. Le chloralose aurait pour principal effet de diminuer la phase postérieure à l'activité pendant laquelle les structures thalamiques et corticales impliquées dans le système associatif étudié sont irresponsives. Il est difficile de dire si cette action est due à une accélération de la phase de récupération ou bien (comme nous avons tendance à le penser) s'il ne s'agirait pas plutôt de la suppression de processus d'inhibition qui s'exerceraient normalement chez l'animal éveillé sur certains relais thalamiques, parmi lesquels le centre médian.

Ajoutons enfin que, dans le relais spécifique du thalamus comme sur le cortex primaire, on peut en présence de chloralose, mettre en évidence la somatotopie déjà décrite chez le singe sous Nembutal (Woolsey, Marshall et Bard 1942; Mountcastle et Henneman 1952). Les réponses restent bien individualisées; leur fatigabilité est du même ordre

avec les deux types d'anesthésie, ce qui écarte l'objection que le chloralose pourrait perturber au même titre tous les systèmes de projection et met en évidence son action élective sur le système associatif.

b) Le centre médian et la zona incerta du singe se comportent d'autre part vis-à-vis des stimulations périphériques comme le font ces noyaux chez le chat. On y observe en effet la convergence des signaux hétérotopes dans l'ensemble du noyau. Enfin, la stimulation du CM provoque des réponses, chez le macaque, dans la région associative frontale que nous venons de décrire, comme elle en provoquait chez le chat dans les quatre zones associatives (Albe-Fessard et Rougeul 1958). Ces faits sont en faveur de l'attribution à cette structure thalamique d'un rôle de relais sur une voie somesthésique secondaire. Cependant, le nombre d'animaux dont nous disposions était trop restreint pour qu'il soit possible, par une étude des latences, d'étayer cette hypothèse aussi rigoureusement que nous avions pu le faire chez le chat. Les écarts de latence observés dans nos quelques mesures peuvent avoir diverses explications. Nous avons trouvé plus difficile de maintenir parfaitement constante la température centrale du singe que celle du chat, parfois la température de nos singes est descendue à 36° ; or, les latences des réponses CM-cortex sont, nous l'avons vu chez le chat, très sensibles aux variations de température ; nos écarts temporels ont peut-être cette origine. Le noyau centre médian chez le singe est d'autre part plus étendu que celui du chat ; par conséquent, les stimulations que nous avons pratiquées par une électrode bipolaire sont moins globales, ce qui entraîne peut-être une plus longue latence dans la liaison CM-cortex. Enfin, le nombre restreint des mesures nous interdit tout traitement statistique. Nous avons donc malgré tout de fortes présomptions pour penser que le CM joue chez le macaque un rôle analogue à celui que nous lui avons attribué chez le chat.

c) La liaison centre médian-cortex est-elle directe ? Les latences relativement longues (nettement plus longues que celles observées chez le chat) que nous trouvons lors de la stimulation du CM ne nous permettent pas de l'affirmer. Nous ne reviendrons pas ici sur les données anatomiques qui plaident contre cette liaison directe. Nous avons déjà discuté ce point dans notre travail sur le chat auquel nous renvoyons (Albe-Fessard et Rougeul 1958).

d) Ajoutons enfin que nous n'avons pu étudier les types d'afférences cutanées, musculaires ou de la sensibilité profonde qui correspondent à ce système de projection. Les différences de latences correspondant aux stimulations des pattes antérieures ou postérieures sont du même ordre pour l'aire frontale et pour les aires primaires (voir tableau). Cela montre en tout cas que des fibres à conduction rapide participent largement à ce système.

RÉSUMÉ

1° — Une même stimulation électrique des téguments provoque, au niveau du cortex non-enfoui du macaque anesthésié au chloralose, des réponses dans les gyrus postcentral, précentral, temporal supérieur, frontal supérieur et l'aire pariétale associative. Ces réponses bien individualisées sont séparées par des zones de silence.

2° — Les réponses non-primaires observées au niveau du gyrus frontal et dans l'aire pariétale associative n'avaient pas été décrites jusqu'à présent. Elles seules ont la propriété d'être évoquées par des stimulations somatiques de diverses origines. Les régions impliquées sont donc des lieux de convergence faisant partie de zones plus larges où s'observent des activités spontanées de grande amplitude.

3° — Au niveau du centre médian du thalamus et dans la zona incerta, des réponses qui ont, elles aussi, des propriétés de convergence peuvent être observées dans les mêmes conditions de stimulation périphérique.

4° — La stimulation du centre médian provoque dans le gyrus frontal des réponses dont les latences sont relativement longues, ce qui ne permet pas de conclure sans réserves à une connexion directe centre médian-cortex frontal, connexion qui n'a d'ailleurs jamais été reconnue par les histologistes.

5° — Les points suivants sont discutés: mécanisme d'action possible du chloralose permettant la mise en évidence de ces activités, et rôle de relais du centre médian sur la voie afférente secondaire vers les aires frontales.

SUMMARY

1. One same electrical stimulation of the teguments in monkeys anesthetized with chloralose gives rise on the non-buried cortex to responses in the postcentral, precentral, temporalis superior and frontalis superior gyri, and in the associative parietal areas. These well-individualized responses are separated by silent zones.

2. The non-primary responses observed at the level of the frontal gyrus and in the associative parietal area had not yet been described. Only these have the property of being evoked by somatic stimulations from different origins. The regions involved are thus sites of convergence, these being part of the wider zones where intense spontaneous activities are observed.

3. Responses endowed with converging properties can also be found in centrum medianum nucleus of the thalamus and in the zona incerta under the same conditions of peripheral stimulation.

4. Stimulation of the centrum medianum n. evokes in the frontal gyrus responses of relatively long latencies; this makes it difficult to assume the existence of a direct connection between this nucleus and the frontal cortex, a connection that has never been recognized by histologists.

5. The following points are discussed: possible mechanism of action of chloralose as revealing such activities as were described here, and role of centrum medianum nucleus as a relay along the secondary afferent pathways towards the frontal areas.

ZUSAMMENFASSUNG

1. Bei Affen unter Chloralose-Narkose provoziert ein und dieselbe Reizung der Haut Reizantworten in der nichteingefalteten Rinde der Postzentral- und Präzentralregion, der oberen Schläfenwindung, der oberen Stirnwindungen und des parietalen Assoziationsfelder. Diese gut definierten Reizantworten werden in Rindenfeldern registriert, welche von einander durch stumme Zonen getrennt sind.

2. Die nicht-primären Reizantworten, welche in der Frontalwindung und im assoziativen Parietalfeld beobachtet wurden, sind bis jetzt noch nicht beschrieben worden. Nur diese Reizantworten haben die Eigenschaft, durch somatische Reize verschiedener Provenienz hervorgerufen zu werden. Die Rindenfelder, wo diese Reizantworten auftreten, müssen daher als Konvergenzareale angesehen werden und diese selbst bilden einen Teil einer weiteren Zone, in welcher intensive Spontanaktivität beobachtet wird.

3. Reizantworten, welche Konvergenzeigenschaften aufweisen, werden auch im Centrum medianum des Thalamus und in der Zona incerta registriert und zwar unter denselben peripheren Reizbedingungen, unter welchen man die Rindenantworten findet.

4. Reizung des Centrum medianum erzeugt eine Reizantwort in der Stirnwindung, welche durch eine lange Latenzzeit charakterisiert ist. Dies lässt die Existenz einer direkten Verbindung zwischen diesem Kern und der Stirnrinde als unwahrscheinlich erscheinen und eine solche Verbindung ist auch niemals von Histologen beschrieben worden.

5. Die folgenden Aspekte werden besprochen: (a) Der mögliche Mechanismus der Chloralosewirkung, welche dem Auftreten von Aktivitäten zugrunde liegt, wie sie in dieser Arbeit beschrieben werden, und (b) die Rolle des Centrum medianum als eine Verbindungsstation im Verlauf von sekundären, afferenten Bahnen zum Stirnhirn.

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CLINICAL AND LABORATORY NOTES

Edited by R. S. SCHWAB, M.B. and H. FISCHGOLD, M.D.

LOCALIZATION OF CEREBRAL NEOPLASM BY ELECTROENCEPHALOGRAPHIC RECORDING AFTER BARBITURATE INJECTION; CASE REPORT [1]

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(Received for publication: November 20, 1958)

The purpose of this communication is to emphasize the localizing value of decreased or absent fast activity recorded electroencephalographically after premedication with barbiturates. Silverman and Groff (1957) reported that in several cases of superficial cerebral neoplasm, a delta or theta focus persisted during sleep. There was frequently an associated suppression of sleep activity and in a few cases barbiturate spindling was decreased or absent in the area of slowing.

Recently two children were studied in this clinic, each of whom was later found to have an astrocytoma of the right cerebral hemisphere at craniotomy. EEG's recorded after intramuscular pentobarbital injection revealed an absence of fast activity in the right scalp leads, with preservation of the barbiturate spindling in the left. These cases will be reported in detail.

CASE REPORTS

Case 1.

A seven month old male was admitted for evaluation of retarded development. There was no history of maternal infection or illness during pregnancy. The delivery and postnatal course had been unremarkable. The child had never gained head control, did not roll over, and did not follow moving objects with his eyes. His weight gain had been normal. Examination on admission revealed a lethargic disinterested child with a shrill cry. The head was not enlarged. The anterior fontanel was open but not bulging. The fundi were normal. Extraocular movements were normal although he failed to consistently follow moving objects. He moved all extremities well. The deep tendon reflexes were hyperactive but bilaterally equal. The plantars were extensor bilaterally. X-rays of the skull were within normal limits. There was no evidence of increased intracranial pressure. An EEG recorded during light sleep after i.m. pentobarbital disclosed high voltage slow waves in the right scalp leads. In addition, 22 to 24 c/sec. activity conspicuously present in the left leads was absent on the right (fig. 1).

A right occipital burr hole was made in preparation for ventriculography. When the needle was introduced a firm mass was immediately encountered. A right parieto-occipital craniotomy revealed an infiltrating neoplasm, which appeared to involve the entire right cerebral hemisphere. Microscopic examination disclosed the tumor consisted of mature astrocytes and fibrils.

Case 2.

A five year old male was admitted because of persistent vomiting. One year prior to admission he was noticed to be less active than usual and he began to have recurrent bouts of vomiting. Headache, primarily frontal, became more frequent. Three months prior to admission an increasing weakness of the left arm and leg was noticed, as well as an enlargement of the head.

Past history was unremarkable. His growth and development had been normal until the present illness.

Examination on admission revealed a lethargic child with a spastic left hemiparesis. The head appeared enlarged, and there was a left facial weakness. There was no papilledema. X-rays of the skull showed a widening of the sagittal and coronal sutures and an erosion of the posterior clinoids. A right frontal calcification was also observed. An EEG recorded during light sleep revealed high voltage slow waves bilaterally. There was an absence of fast activity (18 to 20 c/sec.) in the right scalp leads (fig. 2).

A ventriculogram revealed a marked displacement of the right lateral ventricle to the left. At craniotomy, the entire right cerebral hemisphere was involved by a neoplastic process. Microscopic examination of resected tissue disclosed an infiltrating tumor composed of mature appearing astrocytes.

DISCUSSION

During drowsiness induced in a normal subject by barbiturates the alpha waves were gradually reduced in amplitude and continuity, and rapid activity of 20 to 30 c/sec. appeared, first in the frontal leads. The fast waves spreaded posteriorly and became continuous in all leads. There next occured a slowing to 15 c/sec. with increased amplitude, especially in the

[1] The opinions expressed in this paper are those of the author and do not reflect the policy of the Navy Department.

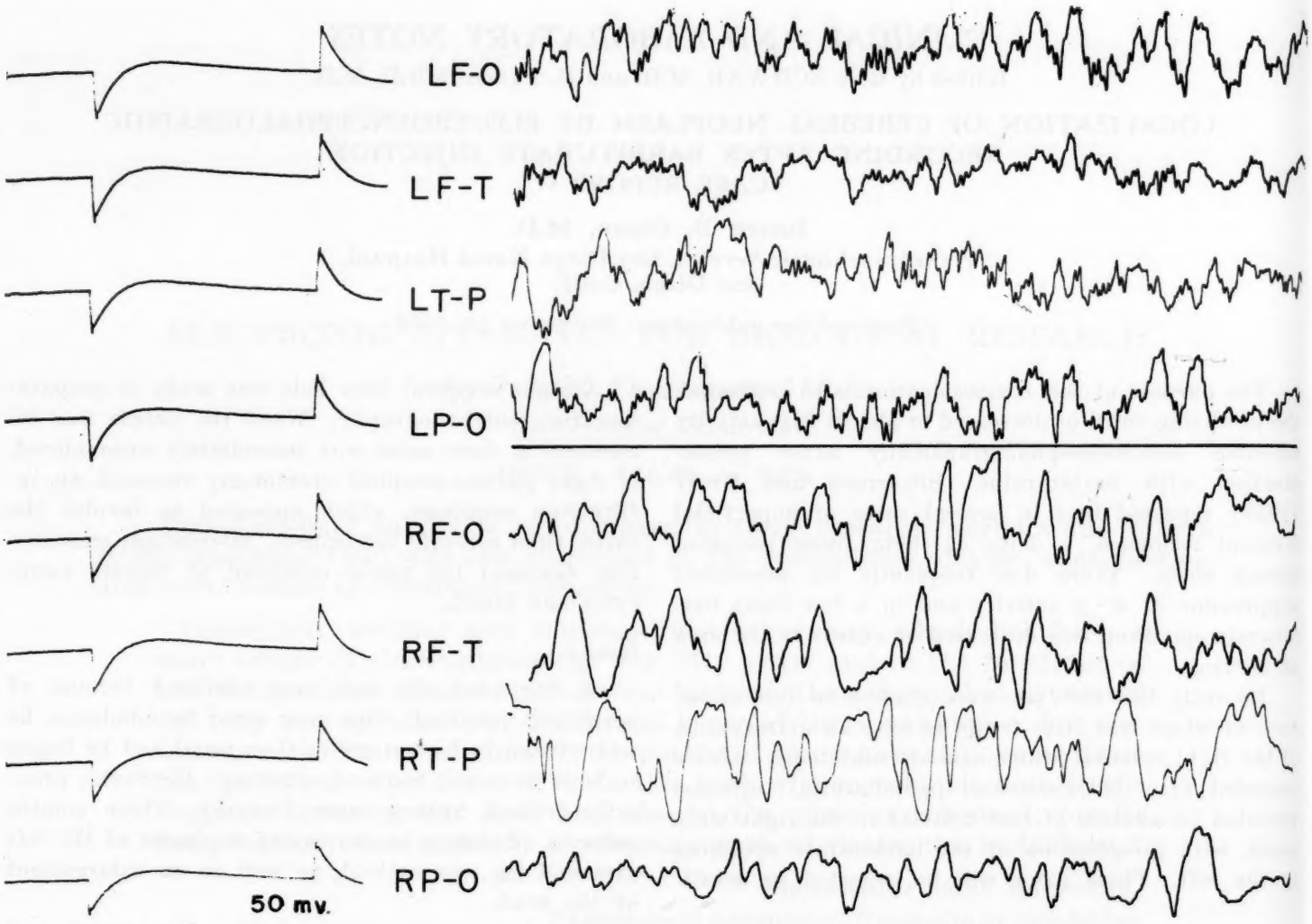

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Fig. 1

Seven month old male with infiltrating astrocytoma of right cerebral hemisphere. Note persistent slow focus and absent fast activity on the involved side (sedation: Pentobarbital 1 gr. i.m.).

frontal regions. These changes have been described in detail (Brazier and Finesinger 1945; Shimazono *et al.* 1953). Evidence has been presented that the thalamus may be responsible at least for the slower type of barbiturate activity through a process of cortical activation.

Shimazono *et al.* (1953) showed that alterations of cerebral function caused by hypoglycemia and ECT were reflected in the EEG not only by slowing, but also by a failure of rapid activity to appear after the i.v. administration of sodium Amytal. The restoration of brain function to normal permitted the appearance of these fast waves. Shimazono *et al.* concluded that the function of the brain had to be maintained above a certain level for fast activity to appear after barbiturate injection.

In common with the reversible effects of hypoglycemia and ECT, the extensive neoplasms in the cases reported were associated with slowing and absence of fast activity. The uninvolved hemisphere in each case retained responsiveness to the injected barbiturate with the development of 18 to 24 c/sec. waves. The hypothesis of Shimazono *et al.* may be modified to include localized areas, where reduced function may prevent the development of the barbiturate effect. In the case of neoplasm, the anatomic substrate of this activity may be destroyed, either by infiltration and replacement of the cerebral cortex, or possibly by invasion of the thalamus. From a clinical standpoint, the unilateral absence of rapid barbiturate activity was helpful in tumor localization, especially in case 2 where slowing was bilateral, presumably because of increased intracranial pressure. It may well be desirable in certain patients with increased intracranial pressure to precede electroencephalographic recording by injection of a barbiturate.

SUMMARY

Fast activity between, 18 and 22 c/sec. occuring in the EEG's of 2 children receiving barbiturate premedication was obliterated on the side of a neoplasm verified at operation. The barbiturate activity was conspicuously present on the side not involved with tumor.

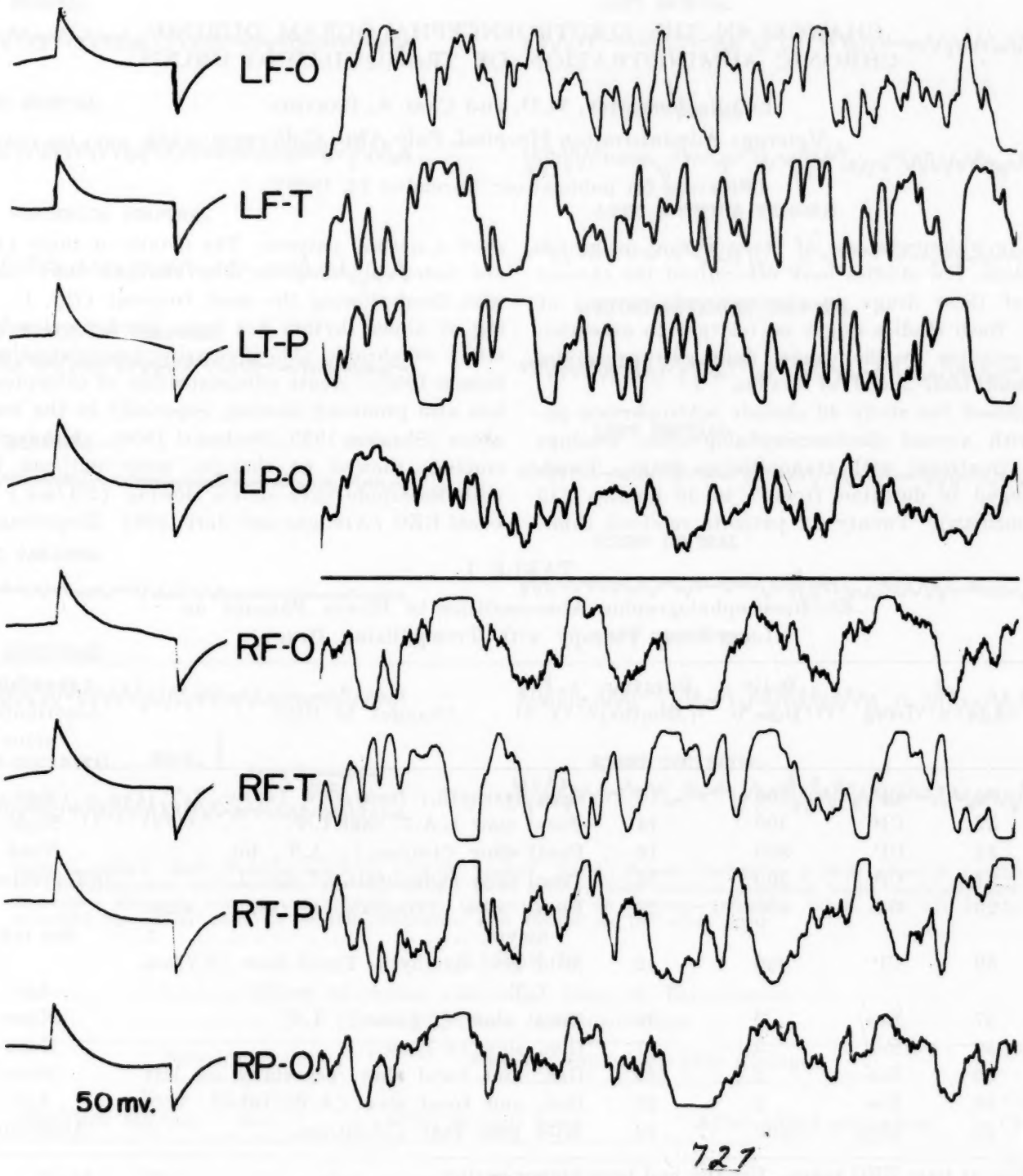

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Fig. 2

Five year old male with infiltrating astrocytoma of right cerebral hemisphere. On bipolar recording high voltage slow waves are noted bilaterally, as well as an absence of faster activity on the involved side (sedation : Pentobarbital 3 gr. i.m.).

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CHANGES IN THE ELECTROENCEPHALOGRAM DURING CHRONIC ADMINISTRATION OF TRANQUILIZING DRUGS

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(Received for publication: December 13, 1958)

Despite widespread use of tranquilizing drugs for long periods, few studies have determined the chronic effects of these drugs on electroencephalograms of patients. Such studies might be relevant to exacerbation of seizures by the drugs, their extrapyramidal effects and their mode of action.

We chosed for study 40 chronic schizophrenic patients with normal electroencephalographic tracings prior to treatment with tranquilizing drugs. Treatment ranged in duration from 7 to 36 months (15 months median). Twenty-six patients received chlorpromazine 100 to 800 mg. daily (median 400 mg.), 10 Reserpine 2 to 10 mg. daily (median 1200 mg.). Both pre- and post-treatment electroencephalograms were read independently by each of two observers, one of whom was unaware of the sequence of the tracings or the identity of the patients.

Eleven patients had changes toward an abnormal EEG pattern, the other 29 patients continuing to show a normal pattern. The details of these 11 cases are noted in table I. The changes were variable, with focal slowing the most frequent (fig. 1). Slowing of alpha rhythm has been noted previously in a study of chronic chlorpromazine administration (Liberson 1955). Acute administration of chlorpromazine has also produced slowing, especially in the temporal areas (Shagass 1955; Szatmari 1956). Although scalp tracings showed no changes, some patients treated with Reserpine have shown slowing (2-3/sec.) in the basal EEG (Arellano and Jeri 1956). Meprobamate in single oral doses of 1600 to 2000 mg. produced low voltage (20-30/sec.) fast activity resembling that from barbiturates (Pfeiffer *et al.* 1957).

TABLE I

Electroencephalographic Abnormalities in Eleven Patients on Long-Term Therapy with Tranquilizing Drugs

Case	Age	Drug	Daily Dose *	Duration (Months)	Changes in EEG	Possible contributing factor
1	62	CP	400	16	Gen. dysrhyth.; focal slow (4/sec. L.T.)	Age
2	57	CP	300	14	Focal slow L.A.T. and L.T.	None
3	31	CP	800	16	Focal slow (4-6/sec.); A.T., bil.	None
4	31	CP	200	15	Focal slow (temporals 4-7/sec. L.)	IST previously
5	25	CP	400	29	Focal slow (frontals 4-7/sec.); amp. assym. L	See text
6	59	CP	200	12	Mild gen. dysrhyth. Focal slow (5-7/ses L.T.)	Age
7	57	Res	2	36	Focal slow (2-3/sec.); L.F.	None
8	32	Res	3	27	Gen. slow (6-7/sec.)	None
9	32	Res	2	24	Gen. and focal slow, especially on left	None
10	58	Res	1	26	Gen. and focal slow (A.T., bil.)	Age
11	52	Mep	1200	10	Mild gen. fast (15-20/sec.)	Alcoholism

* Dose at time EEG taken. Usually had been higher earlier.
CP: chlorpromazine — Res: Reserpine — Mep: meprobamate.

There was no correlation between the degree of clinical improvement produced by tranquilizing drugs and the presence or absence of electroencephalographic changes. As is usual after prolonged administration of these agents, none of the patients showed clinical evidences of oversedation or excessive sleepiness. It should be emphasized that factors other than the drugs might have contributed to the changes noted. Previous convulsive therapy, alcoholism, or advancing

The authors wish to express their appreciation to Dr. Richard Wortington and to G. Lawrence Mowery, who read the tracings.

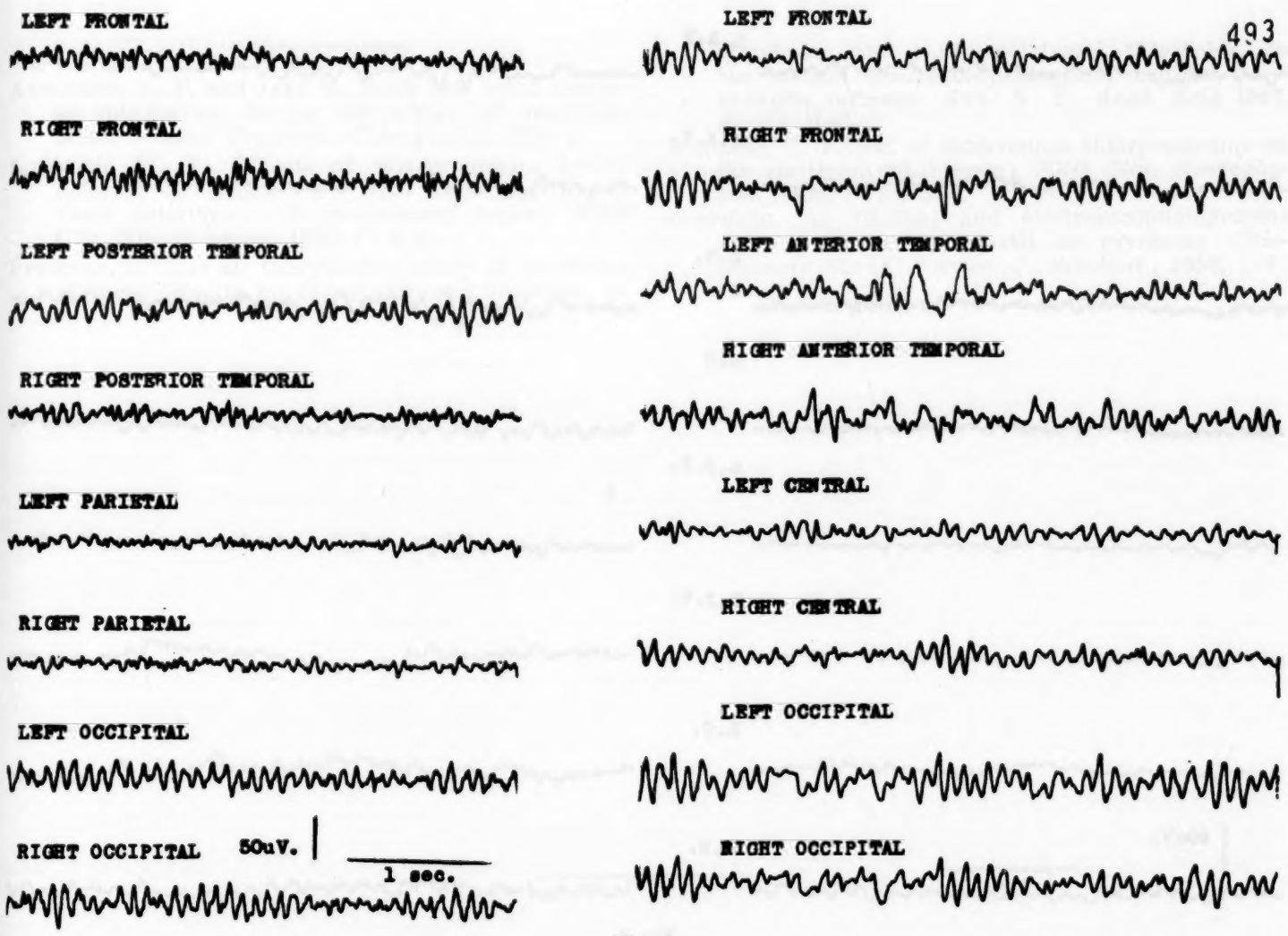

Fig. 1

Case 3, table I. Left: Tracing taken on 4-10-56, normal. Right: Repeat tracing on 9-10-57 after 16 months of chlorpromazine (current dose 800 mg. daily), focal slowing both anterior temporal leads, especially left. Reference electrode consists of 220,000 ohms resistance as an average reference taken, and all of the so-called monopolar runs go to this resistance and thence to the other grid.

TABLE II

Effect of Acute (500 mg) Dose of Thioridazine
During Chronic Administration

		Thioridazine		Electroencephalographic Changes		
Case	Age/Sex	Dose mg/day	Duration mos.	After chronic dose	After added acute dose	Clinical Changes
1	27/M	500	5	Gen. parox. slow (3-6/s)	Same	Marked Imp.
2	34/M	200	5	Normal	Same	Slight Imp.
3	42/M	450	2	Mild gen. slow (5-6/s)	Normal	Moderate Imp.
4	25/M	300	4	Normal	Gen. and foc. slow (2-5/sec.)	Marked Imp.
5	48/M	600	4	Minimal slow, LAT	Foc. slow, AT	Unchanged
6	45/M	150	6	Normal	Same	Slight Imp.
7	22/M	600	5	Normal	Foc. slow, LC, LAT	Moderate Imp.
8	46/M	200	5	Normal	Normal	Moderate Imp.
9	49/M	200	5	Parox. slow (4-5/s)	Parox. slow (2-5/sec.)	Unchanged
10	27/M	200	4	Foc. slow (4-6/s), LPT, LO	Gen. and foc. slow (2-6/sec.)	Marked Imp.

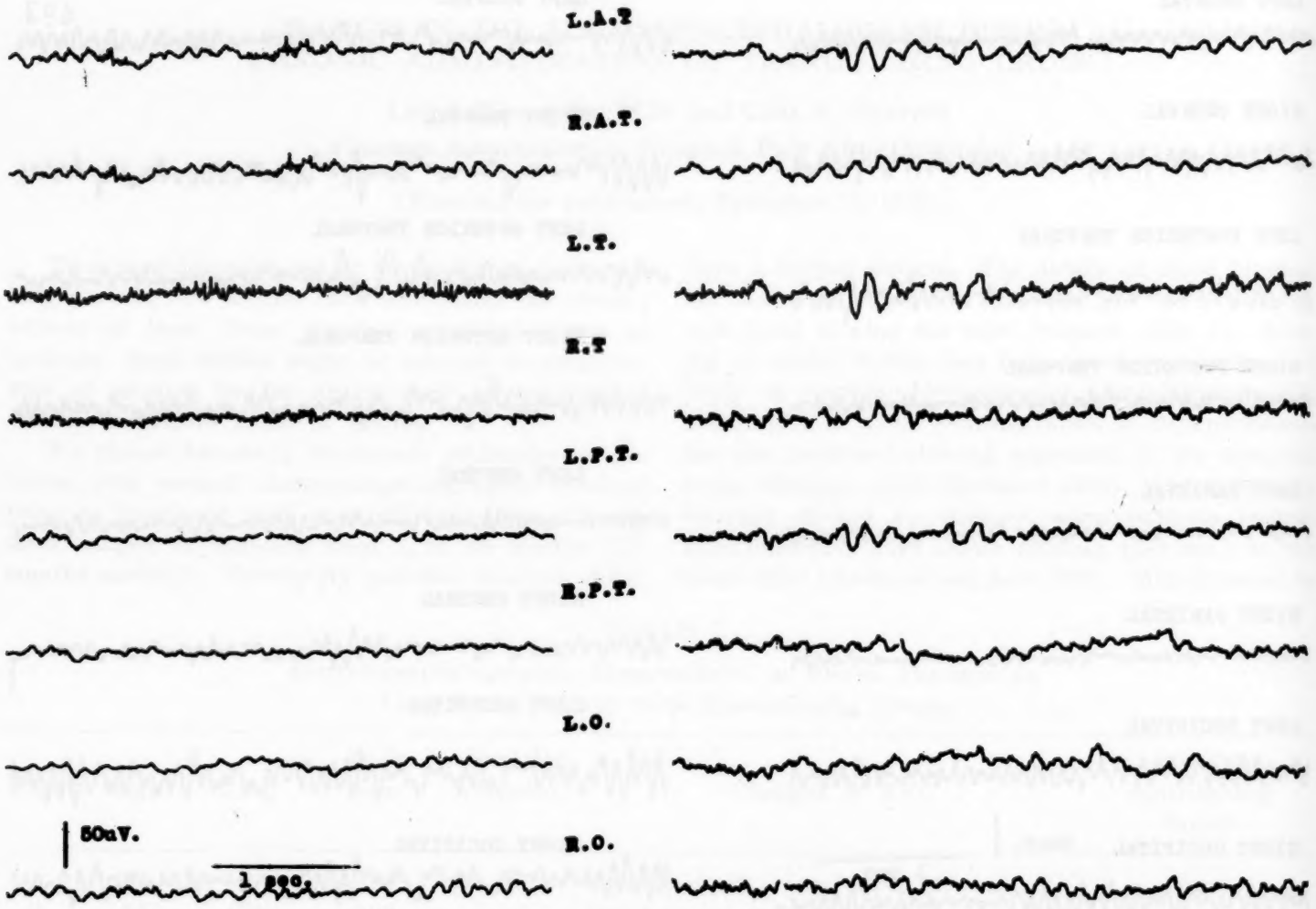

Fig. 2

Case 4, table II. Left: Tracing taken on 12-8-58 after 4 months of thioridazine (current dose 300 mg. daily), normal. Right: Tracing same day, 4 hrs. after added acute dose of 500 mg., generalized and focal slowing, especially on left side.
Reference electrode consists of 220,000 ohms resistance as an average reference taken, and all of the so-called monopolar runs go to this resistance and thence to the other grid.

years are factors to be reckoned with. None of these patients had a history of epilepsy, though one (case 5) had a seizure accompanying a severe extra-pyramidal syndrome during an earlier period of intensive chlorpromazine therapy.

A new phenothiazine derivative, thioridazine, is of interest because it does not produce any extrapyramidal effects. For this reason, electroencephalograms were obtained on 10 schizophrenic patients who had been chronically treated with the drug. Immediately after these tracings were obtained, an additional 500 mg. dose of the drug was administered. Four hours later, another tracing was obtained. All tracings were read blindly.

The results are shown in table II. Five patients had changes (generalized or focal slowing) after chronic administration of thioridazine similar to those observed after chronic treatment with chlorpromazine or Reserpine. When the added acute dose was given, the changes were made worse in all but one case. Abnormalities not present on the initial tracing were elicited by the acute dose in 2 cases (fig. 2). Both these patients showed evident drowsiness of moderate degree following the acute dose of drug. As with the other drugs, there was no correlation between the effect of the drug on the psychosis and the occurrence of electroencephalographic abnormalities.

CONCLUSION

Chronic administration of tranquilizing drugs in therapeutic doses may be associated with electroencephalographic abnormalities. In the case of chlorpromazine and Reserpine, generalized dysrhythmia and focal slowing are most commonly observed. Similar changes follow chronic treatment with thioridazine, a drug which does not produce extrapyramidal effects. The significance of these changes is not known, but their presence may lead to diagnostic confusion unless considered as a possible drug effect. Further studies of the chronic effects of these drugs on electroencephalographic patterns should be done.

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ELECTROENCEPHALOGRAPHIC FINDINGS ASSOCIATED WITH SERNYL INFUSION

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INTRODUCTION

Sernyl, 1(1-phenylcyclohexyl) piperidine monohydrochloride, was introduced in 1957 as an anesthetic agent (Greifenstein 1958; Chen 1958). Intravenous administration by continuous drip in doses of 0.25 mg. per kg. rapidly produced a profound loss of pain sensation which permitted the performance of minor and even major surgical procedures without recourse to other standard anesthetic agents. The patient appeared not to be unconscious, but rather in a state similar to what is known in the neurological literature as akinetic mutism. The patient would lie with his eyes open, immobile, at times looking at the examiner, but not responding to questions or painful stimuli. When the patient's arm was passively moved, it might retain the given posture in a catatonic fashion. Although surgery could be done without discomfort to the patient, the usefulness of the drug as an anesthetic was limited by the acute psychotic reactions which frequently ensued and which lasted up to about 18 hours (Meyer *et al.* 1958). One patient, however, remained in a semiconscious state for 10 days.

Sernyl [1] was investigated as a psychotomimetic agent by Luby *et al.* (1958). After intravenous administration in varying doses, it produced severe depersonalization, feelings of unreality, a thinking defect characterized by concreteness and loosening of associations, hypnagogic states, repetitive motor phenomena, and feelings of inebriation. Sernyl seemed to reproduce the primary symptoms of the schizophrenic process. The present report deals with the electroencephalographic findings.

METHOD

Fourteen nonpsychotic psychiatric patients and 6 normal volunteer subjects were given intravenous infusions of Sernyl. The procedure was usually begun at 9 a.m. with the patient in the fasting state. After a routine 15 min. baseline EEG tracing, an intravenous drip of 5 per cent dextrose in water was started. After 5 min. the flow was shifted to Sernyl in a glucose water solution. The patient had his eyes closed and was unaware of the fact that one infusion had been stopped and another started. The EEG was recorded for the earlier subjects on an Edin 8 channel electroencephalograph and for the later subjects on an 8 channel Type T Offner transistor electroencephalograph. Fourteen electrodes applied with bentonite were used in bipolar connections.

Three different dosage levels of Sernyl were utilized in different individuals, the maximum dose being 0.2 mg. per kg., a medium dose of 0.1 mg. per kg., and a minimal dose 0.03 mg. per kg. The infusion rate was kept constant and the total dose was given over a 12 min. period.

RESULTS

Maximum Dose

Eleven individuals received the maximum dose. There were 2 normal volunteers with normal resting EEGs, 6 patients with normal resting EEGs, and 3 patients with slightly disorganized resting EEGs containing a marked mixture of frequencies. After Sernyl both volunteers showed marked theta activity, a medium voltage 4 to 5 c/sec. rhythm becoming dominant irrespective of whether the subject had his eyes open or closed. Of the 6 patients with normal predrug EEGs 5 showed marked theta slowing, while one patient's record did not change appreciably. Of the 3 patients whose EEGs were slightly disorganized in the resting state, after Sernyl infusion 2 showed no electroencephalographic change and one showed an increase of slow frequency activity. Figure 1 represents typical examples of induced theta activity.

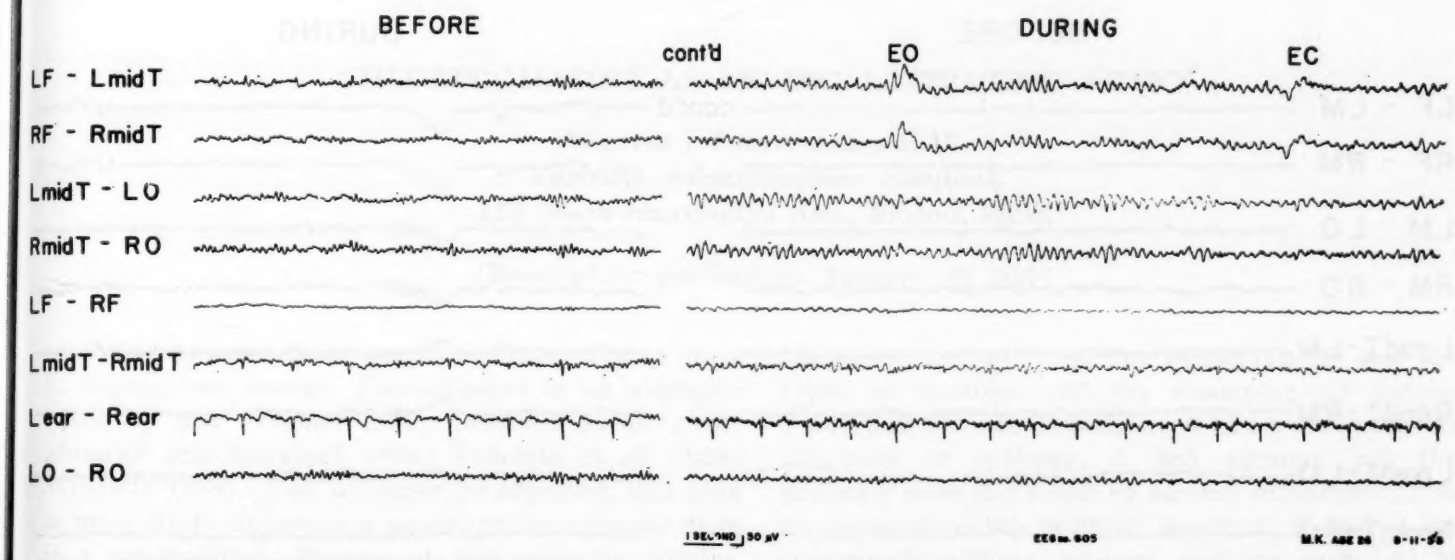
Medium Dose

Four individuals with normal predrug EEGs received 0.1 mg. per kg. These were 2 volunteer subjects and 2 patients. One volunteer showed slowing to the 5 to 7 c/sec. frequency range, while the other did not. One patient also showed slowing, while the other did not.

Minimal Dose

Five individuals received the minimal dose of 0.03 mg. per kg. Four of these were normal volunteers and one was a patient with a temporal lobe convulsive disorder and sharp wave focus in the left temporal

[1] We are indebted to Parke, Davis & Co. for kindly supplying the Sernyl used in this study.



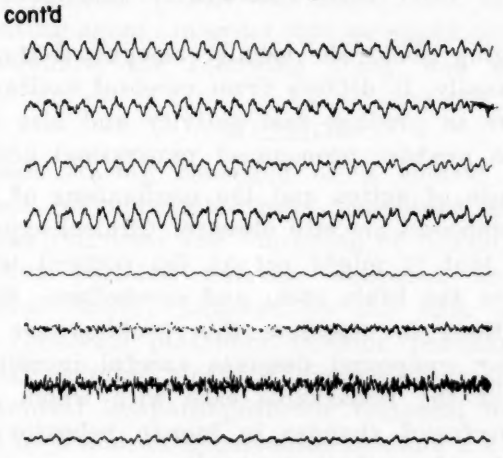


Fig. 1

Typical EEG changes resulting from intravenous infusion of 0.2 mg. per kg. of Sernyl. Note the pronounced theta activity which is not inhibited when the patient has the eyes open.

area. One of the normal volunteers showed slight theta slowing, while the other three showed no appreciable changes. The patient showed no EEG changes either in the way of background activity or in the frequency of firing of the sharp wave discharge.

DISCUSSION

It appears from these observations that Sernyl can produce rather profound slowing of the EEG. The slowest frequencies observed with maximum dosage were between 3 and 4 c/sec. The drug does not seem to induce paroxysmal discharges when they are not present in the resting record, and it does not induce strictly focal abnormalities. The type of onset of slow wave activity varied in different individuals. In some instances the basic alpha frequency gave way to some intermittent 5 to 7 c/sec. waves and somewhat later was replaced completely by this frequency. In other instances a stepwise reduction of frequencies could be observed. A basic 10 to 11 c/sec. alpha rhythm was replaced by an 8 to 9 c/sec. rhythm; this then gave way to 7 to 8 c/sec. activity; which in turn was followed by 5 to 7 c/sec. rhythm. The 8 to 9 c/sec. activity resembled normal alpha rhythm, yet was abnormally slow for the particular individual. Disorganization of the EEG could be induced with equal ease in patients and volunteers. It was likewise not possible to predict from the resting EEG whether it would show marked slowing. Normal records were at times easily disorganized to a pattern of rather ill-defined frequencies, while mildly dysrhythmic records sometimes showed no definite change.

It should be pointed out that psychotomimetic effects were observed in the absence of definitive EEG changes. Where EEG changes occurred, psychic manifestations nearly always preceded them by at least 1 to 2 min. These psychic manifestations consisted mainly of alterations in body image, depersonalization, lability of affect, and difficulties in thinking. All the patients and subjects reported here had pronounced psychic experiences except for 2 individuals who received the minimal dose.

An invariable physiological concomitant of the psychotomimetic effect of this drug was a rise in systolic blood pressure, which usually occurred about 3 to 4 min. after the Sernyl infusion was started. The rise in systolic pressure was followed a few minutes later by a rise in diastolic pressure. The blood pressure began to return to its predrug level about 15 min. after the cessation of the infusion. Subjects with a somewhat higher than average resting blood pressure showed a greater rise with Sernyl infusion than subjects whose resting pressure was around 120/80. The highest blood pressure recorded in this series of experiments was 185/140 in an individual whose resting blood pressure had been 145/95. The usual rise observed was 145/105 from 120/80 in the resting state.

The electroencephalographic effects usually disappeared in a period of 15 to 60 min. after cessation of drug administration, depending upon the amount of drug given and the severity of changes induced. The restitution of the EEG to its predrug level

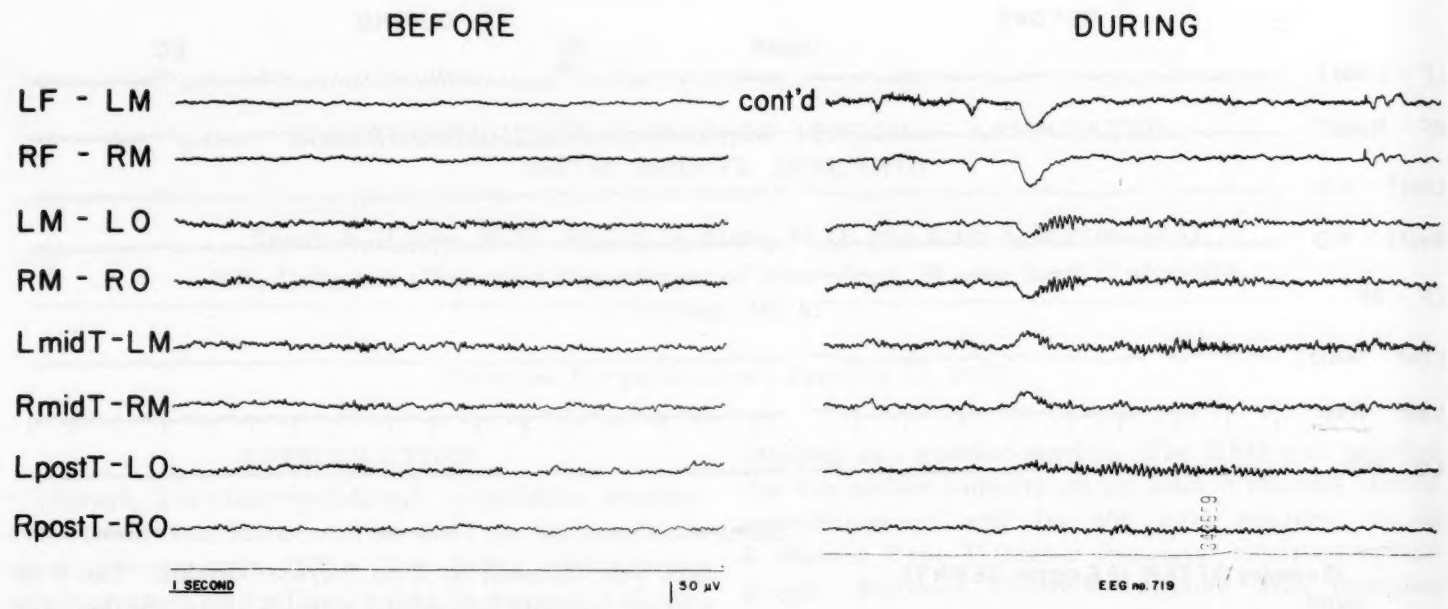


Fig. 2
Theta activity induced by 0.1 mg. per kg. of Sernyl infusion.

occurred in a way similar to its disorganization. It might be stepwise through gradual increase in frequencies, or more abrupt, depending on the way disintegration had come about. The psychic changes definitely outlasted the electroencephalographic and blood pressure changes by several hours.

Sernyl, in the dosages used here, is considerably different from other anesthetic or psychotomimetic agents. Electroencephalographically, it does not produce any of the usual stages of anesthesia. It differs clinically since it does not lead to unconsciousness. It differs also from barbiturates and other sedatives by not bringing about the usually recognized stages of sleep. Finally, it differs from cerebral excitants by its failure to produce fast activity and also by its failure to produce pronounced paroxysmal activity.

The site of action and the mechanisms of action of the compound are still obscure. Clinical experience suggests that it might act at the cortical level as well as on the brain stem and cerebellum. Specific investigations to elucidate this problem are under way. This compound deserves careful investigation because of the remarkable ease with which it can induce profound changes in human behavior which are clearly of psychotic proportions.

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CHLORPROMAZINE AS AN EEG ACTIVATING AGENT

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There appears to be ample evidence that at least in appropriate dosage, phenothiazine is an analeptic (Bradley and Jeavons 1957; Liberson *et al.* 1958; Monnier and Gangloff 1956; Tedeschi *et al.* 1958; Winfield 1958). Too, as might be expected, this drug is more likely to induce a seizure in an epileptic than in a non-epileptic. Because of this analeptic activity, chlorpromazine (CPZ) has been tried as an EEG activating agent; in order that we might evaluate such a procedure, the following study was undertaken.

METHOD

Each tracing consisted of a control record of 2.5 min. of monopolar runs (combined ears as the common reference and consisting of bilateral frontal, posterior parietal, anterior temporal, and central temporal leads), followed by 2.5 min. of bipolar runs (bilateral prefrontal-anterior parietal, anterior parietal-occipital, anterior temporal-central temporal and central temporal-posterior temporal leads), followed by 3 min. of hyperventilation and a 2 min. post-hyperventilation run using the same bipolar runs and followed, lastly, by bipolar runs (bilateral prefrontal-anterior parietal, anterior parietal-occipital, and anterior temporal-posterior temporal leads) during intermittent photic stimulation using flash frequencies of 8, 10, 12 and 16/sec. each for about 7 sec. Immediately after the control run, the patient was given 50, 75 or 100 mg. of CPZ intramuscularly; then, runs similar to those used in the control were repeated 30, 60, 90 and 180 min. later. The patient's blood pressure was determined before the control run was started and again after it was completed; similar blood pressure determinations were obtained before and after each other run. Before and after each run the patient was questioned as to how he felt. An attempt was made to keep the patient awake during all of these tracings; this resulted in varying degrees of lack of success.

Eighty-three tracings were obtained on a total of 81 patients; 55 patients received 50 mg. of CPZ, 12 received 75 mg., and 16 received 100 mg. Two of the epileptic patients who received 50 mg. were subsequently tested with 75 mg. Fifty-six of the patients were definite epileptics and of these 17 had temporal lobe seizures, 6 had questionable temporal lobe seizures, 4 had idiopathic epilepsy, one had questionable idiopathic epilepsy, and the remaining 28 had other types of seizures. Of the remaining 25 patients, 7 had had but one convulsion, 6 had an unestablished diagnosis of epilepsy, 6 had seizures but these probably were the result of alcohol withdrawal, 2 had an encephalopathy without seizures, 2 had a psychoneurosis without epilepsy, and one each had Meniere's syndrome and Adams-Stokes' syndrome. The average age of the patients was 37 years with a range of 20 to 69 years. No attempt was made to stop any anticonvulsant medication which the patient may have been receiving immediately prior to the test.

All patients had at least one routine (waking) EEG within two weeks before the CPZ-EEG; most of the patients also had a sleep (natural or Seconal-induced) and a Metrazol-activated (Friedlander 1954) EEG again within two weeks of the CPZ-EEG.

RESULTS

1. *EEG changes.* Some change in the EEG was seen 20 times in 18 patients following the administration of the CPZ. These findings are summarized in table I. In comparing the post-CPZ tracing with their own control, the EEG changes seen after CPZ were classified as *abnormal* (changes were definite whether because some abnormality was seen in the test run that was not seen in the control, or because the abnormality that had already been seen in the control was definitely increased during the CPZ runs) — 9 tests — or *questionably abnormal* (only a questionable change was seen in the CPZ runs as compared to the control) — 11 tests.

A review of table I shows that of the 18 patients who had *abnormal* or *questionably abnormal* changes in their CPZ-EEG, 8 had normal routine EEG's and/or pre-CPZ-EEG's (cases 3, 5, 6, 7, 11, 12, 13 and 15). Two of these patients — cases 3 and 15 — had generalized convulsions probably secondary to alcohol withdrawal rather than a true epilepsy. In this group of 8 patients, 7 — cases 3, 5, 6, 11, 12, 13 and 15 — had sleep and Metrazol-activated EEG's. Five of these had abnormal sleep EEG's — cases 3, 6, 11, 12 and 13 — and two had abnormal Metrazol-activated EEG's — cases 11 and 13. One patient — case 15 — had an abnormal routine EEG even though the pre-CPZ, the sleep and the Metrazol-

TABLE I

The various EEG findings in the 18 patients who showed some change during their CPZ-EEG together with the type of seizure, the amount of CPZ given and the state of lethargy at the time the CPZ induced changes were noted.

Case	Type of Seizure	Am't CPZ Given	ELECTROENCEPHALOGRAMS
1.	Gen. convul.; ? temporal lobe	100	*Routine*: abnormal because of right temporal theta/spike and left temporal spike foci; *Sleep*: abnormal because of random spike activity; *Pre*-CPZ: abnormal because of random theta/sharp wave activity; CPZ: increase in right temporal spike activity (awake and drowsy).
2.	Gen convul.; temporal lobe	100	*Routine*: abnormal because of paroxysmal discharge in right anterior-central temporal area; *Sleep*: abnormal because of right anterior temporal spike focus; *Pre*-CPZ: abnormal because of random theta and right anterior-central temporal theta/spike focus; CPZ: increase in right temporal spike focus (drowsy).
3.	? alc. withd. convulsions	100	*Routine*: normal; *Sleep*: abnormal because of bilateral anterior temporal spike foci; *Metrazol*: normal; *Pre*-CPZ: normal; *CPZ*: increase in right temporal spike activity (drowsy).
4.	one gen. convulsion	100	*Routine*: abnormal because of left anterior temporal delta/theta focus; *Sleep*: abnormal because of left temporal theta and left anterior temporal spike foci; *Metrazol*: abnormal because of increase in left central temporal spike focus; *Pre*-CPZ: abnormal because of left temporal theta focus; CPZ: questionable increase in left temporal spike focus (drowsy).
5.	gen. convul.; temporal lobe	75	*Routine*: normal; *Sleep*: normal; *Metrazol*: normal; *Pre*-CPZ: normal; CPZ: moderate "build-up" with hyperventilation.
6.	gen. convul.	75	*Routine*: normal; *Sleep*: abnormal because of left anterior temporal spike focus; *Metrazol*: normal; *Pre*-CPZ: questionably abnormal because of questionable left anterior-central temporal theta focus; CPZ: questionable increase in theta focus (awake and drowsy).
7.	gen. convul.; focal motor	50	*Routine*: normal; *Pre*-CPZ: normal; CPZ: spike activity on right (awake and drowsy).
8.	gen. convul.	500	*Routine*: abnormal because of left anterior-central temporal theta focus; *Sleep*: abnormal because of left anterior-central temporal theta focus; *Metrazol*: abnormal because of "build-up" in left anterior-central temporal area and production of seizure after 300 mg. *Pre*-CPZ: abnormal because of left temporal theta/delta focus; CPZ: increase in spike activity in left temporal focus (drowsy).
9.	gen. convul.	50	*Routine*: abnormal because of right sided spike-wave activity; *Sleep*: abnormal because of spike activity on the right; *Pre*-CPZ: abnormal because of right sided spike-wave activity; CPZ: increase in spike-wave activity on the right (awake).
10.	? alc. withd. convulsions	50	*Routine*: abnormal because of right posterior theta focus; *Sleep*: abnormal because of right sided spike focus; *Metrazol*: abnormal because of non-focal paroxysmal burst after 400 mg.; *Pre*-CPZ: abnormal because of right posterior theta focus; CPZ: non-focal spike-wave activity during hyperventilation.
11.	gen. convul.; focal motor	75	*Routine*: abnormal because of left anterior wave bursts; *Pre*-CPZ: abnormal because of anterior spike-wave bursts; CPZ: questionable increase in spike-wave bursts (awake).
		50	*Routine*: normal; *Sleep*: abnormal because of bilateral spike foci; *Metrazol*: abnormal because of non-paroxysmal theta focus on left after 175 mg.; *Pre*-CPZ: normal; CPZ: spike-wave bursts without focus (drowsy).
12.	gen. convul.	50	*Routine*: normal; *Sleep*: abnormal because of spikewave complexes in the right anterior area; *Metrazol*: abnormal because of paroxysmal activity without focus after 250 mg.; *Pre*-CPZ: normal; CPZ: paroxysmal delta/spike-wave on the right (awake/drowsy).
13.	gen. convul. temporal lobe	50	*Routine*: normal; *Sleep*: abnormal because of spike focus in left anterior temporal area; *Metrazol*: normal; *Pre*-CPZ: normal; CPZ: had an olfactory hallucination without EEG changes (awake).

14.	gen. convul.; temporal lobe	50	*Routine*: abnormal because of sharp wave and paroxysmal right sided focus; *Metrazol*: abnormal because of paroxysmal bursts questionably better defined on the right after 100 mg.; *Pre*-CPZ: abnormal because of sharp wave and paroxysmal right sided focus; CPZ: questionable increase in paroxysmal bursts (awake).
15.	? alc. withd. convulsions	50	*Routine*: abnormal because of spikey and paroxysmal activity without focus; *Sleep*: normal; *Metrazol*: normal; *Pre*-CPZ: normal; CPZ: few poorly delineated non-focal paroxysmal bursts (drowsy).
16.	Temporal lobe	75	*Routine*: abnormal because of right anterior temporal spike/theta focus; *Sleep*: abnormal because of right anterior temporal spike/theta focus; *Metrazol*: abnormal because of increase in right anterior temporal spike/theta focus; *Pre*-CPZ: abnormal because of right anterior temporal spike/theta focus; CPZ: questionable increase in right temporal spike activity (awake).
		50	*Routine, Sleep, Metrazol, Pre*-CPZ and CPZ the same as with 75 mg. (see above).
17.	Gen. convul.	50	*Routine*: abnormal because of right temporal theta focus; *Sleep*: abnormal because of right temporal spike focus; *Metrazol*: normal; *Pre-CPZ*: abnormal because of right temporal theta/paroxysmal focus; CPZ: questionable increase in the paroxysmal activity in the right temporal area (drowsy).
18.	gen. convul.; temporal lobe	50	*Routine*: abnormal because of left anterior theta/delta focus; *Sleep*: abnormal because of left anterior theta/delta focus; *Metrazol*: abnormal because of increase in left anterior focus; *Pre*-CPZ: abnormal because of left anterior theta/delta focus; CPZ: questionable increase in the focus with some paroxysmal activity (drowsy).

activated EEG's were interpreted as being normal. This then left only 2 patients — cases 5 and 7 — who had some abnormality in their CPZ-EEG without any abnormality in any other EEG's; however, in neither instance could this be said without some qualification. Case 5's only abnormality in the CPZ-EEG was a moderate ''build-up'' during the 180 min. run which could not be considered as anything except a questionably abnormal finding; case 7 had no other EEG studies except the routine and the pre-CPZ-EEG and hence he should have been considered as not having had a complete work-up, electroencephalographically.

At no time was a focus seen in the CPZ-EEG that had not been seen in some other EEG study except case 7 who, as already commented upon, suffered from a rather incomplete EEG study.

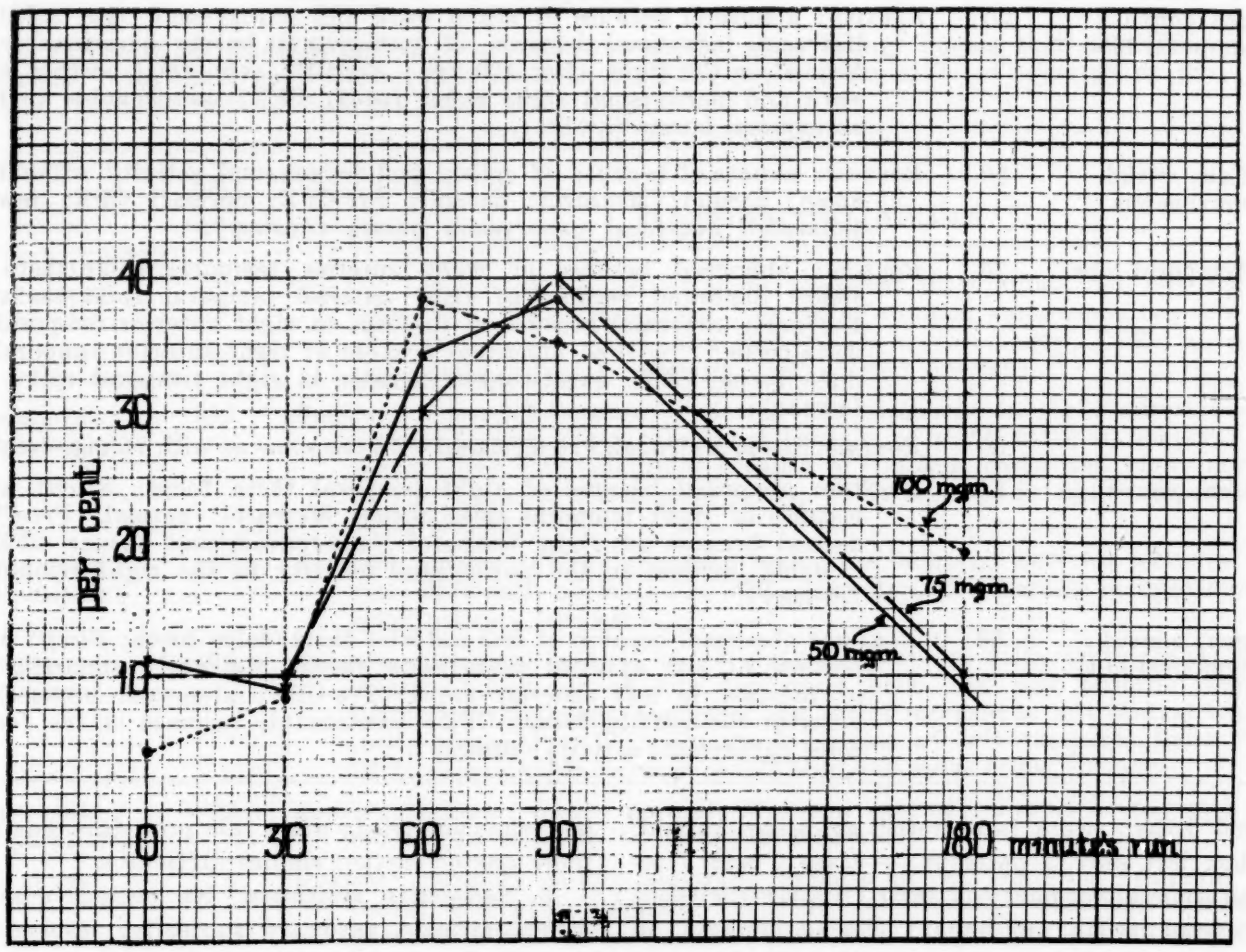
No patient with idiopathic or questionably idiopathic epilepsy had any change in their CPZ-EEG.

2. *Blood pressure changes.* There was a drop in systolic blood pressure of 20 or more mm. of mercury in 8 patients but the greatest drop was only 30. The diastolic pressure never dropped more than 10. No EEG changes were seen associated with these drops in blood pressure. The average age of these 8 patients was 38 with a range of 25 to 63. A 20 mm. or more drop in systolic pressure was seen in 2 patients who received 50 mg. of CPZ, in 3 patients who received 75 mg. and in 3 patients who received 100 mg. Because of several syncopal or near syncopal episodes in patients receiving 100 mg. after they had returned to their wards (i.e. about 3¼ hours after they had been given the CPZ) all the subsequent patients were instructed to remain in bed for 4 hours after the entire test was completed; after this procedure was adopted, there was no further similar difficulty.

3. *Subjective responses.* No patient admitted to any significant untoward subjective response during the test except case 13 who complained of a short period of smelling ''... something funny ... like death''; this occurred during the 60 min. run and after a 50 mg. dose. This patient had epilepsy, symptomatic due to trauma manifested by generalized convulsions and temporal lobe seizures but an olfactory hallucination was foreign to his spontaneous attacks. No particular EEG changes were seen at this time but because of this response, the effect of CPZ was classified as *questionably abnormal.*

4. *Occurrence of drowsiness or sleep.* The relative state of drowsiness or sleep was compared between the various runs in each test. The particular run when there was maximum drowsiness or sleep, as the case may be, was plotted and the results with 50, 75, and 100 mg. doses were thus compared (graph I). The amount of CPZ given did not seem to alter the time when runs in most of the patients showed maximal drowsiness or sleep.

5. *Time of abnormal EEG responses.* When *abnormal* or *questionably abnormal* EEG responses were observed after the administration of CPZ, they were always noted and usually were best delineated in the 30 and/or 60 min. runs even though occasionally they were also seen to some extent in the 90 and 180 runs too. There was only one exception; case 5 had a moderate ''build-up'' during hyperventilation in the 180 min. run whereas no similar EEG changes were seen in his previous 3 CPZ runs.



Graph I

The per cent of patients in each dosage group (50, 75, or 100 mg.) plotted against the various CPZ-EEG runs to indicate in which run there was maximum drowsiness or sleep.

DISCUSSION

It is rather difficult to evaluate most of the reports in the literature (Benassi and Cenacchi 1953; Bente and Itil 1957; Castro and Berard 1954; Lyberi and Last 1956; Simons 1958; Talbot 1958; Szatmari 1956; Turner 1956; Winfield and Aivazian 1958) on the activation of the EEG by CPZ or other phenothiazines since these papers were available to us frequently only as abstracts or were reports wherein "activation" was not the main topic of the paper. The papers of Mayr and Lechner (1954) Fabisch (1957) and Stewart (1957) are exceptions to this and deserve comment.

Mayr and Lechner gave 25 mg. CPZ intravenously to 50 temporal lobe epileptics. All were reported to have had at least a unilateral temporal focus and at least a minimally abnormal EEG. Hence, it may be assumed that examples of activation were really exaggerations of pre-existing abnormalities and therefore nothing that was really new was gained by the CPZ-EEG. Of interest was their comparison of Metrazol, pentathol and CPZ-activations although these tests were apparently done on different groups of patients. They reported activation by CPZ in about 86 per cent of 28 patients and in 36 per cent by Metrazol or in 32 per cent by pentathol in 22 patients. Though these authors felt that CPZ was a useful agent in activating the EEG's of temporal lobe epileptics, they did not compare their results with a control series.

At least initially, we employed the dosage used by Stewart i.e. 50 mg. intramuscularly. In his series of 50 epileptics, he found an *increase* in the EEG abnormalities of 28 epileptics, one patient's EEG improved, and in 5 patients who had a normal pre-CPZ-EEG, the tracing became abnormal. Even though this means that in only 1 out of 10 epileptic patients something new may have been learn from the CPZ-EEG, he concluded that he would "... place chlorpromazine when used together with hyperventilation between barbiturate induced drowsiness activation and that obtained by ... Metrazol ..."; he felt that there was a suggestion of greater usefulness of CPZ-activation in cases of idiopathic epilepsy. Again, there was a lack of non-epileptic controls even though the author felt that this was a useful test in epileptics.

Fabisch's group seemed the best controlled. He gave 0.3-0.5 mg. CPZ/kilo body weight (but not in excess of 25 mg.) intravenously. He had 20 patients without epilepsy, 20 with epilepsy but with a fairly normal interseizure EEG, and 20 with epilepsy but

with a consistently abnormal interseizure EEG. He concluded that CPZ can *increase* the abnormality in the EEG of epileptics though the changes were similar to those seen in the resting interseizure EEG but there was no significant change in patients with or without epilepsy who had normal EEG's.

Our main interest in this or probably any other EEG-activating procedure was to obtain a tool which would help us differentiate the epileptic from the non-epileptic regardless of whether or not he had other neurological disease and/or to define an area of focal pathology which we had not discovered by other EEG techniques. Hence it was decided first to evaluate the effect of CPZ in epileptics and then if this technique seemed of value in this group, to evaluate it further by using an adequate control group. However, the results we obtained with the epileptic group as well as a mixed group of possibly non-epileptic patients with or without seizures did not seem to us to warrant further study. We had begun this investigation with the dosage suggested by Stewart (50 mg. intramuscularly) and then when this had proven unsatisfactory, we increased the amounts of CPZ to as much as 100 mg.; however, our results were still unsatisfactory. In the entire group of 81 patients, the CPZ study did not materially add to our EEG information except in one or perhaps two cases and even then this was only quite questionable. It seems likely then that with the method used in our laboratory and with the patients we had, CPZ is certainly no better than and probably not as good as other techniques which have been better standardized e.g. repeated routine EEG's, sleep EEG's, or Metrazol-activated EEG's.

Since our study was undertaken as a preliminary step in evaluating a new technique of activation, it did not seem warranted to subject the patients to any undue risk which might not be indicated by the limited information that could be gained. Hence in light of Stewart's experience as well as the experience of some of our colleagues in a limited number of patients, we were reluctant to give the CPZ by the intravenous route. The fact that there was a drop of systolic blood pressure of at least 20 mm. of mercury in only 4 per cent of our patients who received but 50 mg. but in 25 per cent of those who received 75 mg. and in 19 per cent of those who received 100 mg. certainly suggested that the larger doses increased the chances of a vasodepressor reaction. The syncopal or near syncopal reactions in several patients who received 100 mg. added further weight to this suggestion. If intramuscular administration could do this, we were rather reluctant to use an intravenous route particularly in light of what seemed to be a poor EEG yield.

All the changes that were seen occurred in the 30 and/or 60 min. runs with only one questionable exception. Hence it would seem reasonable that any further evaluation of CPZ using the method as outlined here could be simplified by obtaining a control run and then repeat tracings at only 30 and 60 min. intervals; too, intermittent photic stimulation could be omitted.

CONCLUSIONS

The efficacy of chlorpromazine as an EEG-activating procedure was examined. Fifty-six epileptics and 25 other patients who did not have a well established diagnosis of epilepsy were given 50 to 100 mg. CPZ intramuscularly; serial EEG tracings were obtained over the ensuing 3¼ hours.

In no case, with two possible exceptions, was any new EEG knowledge gained from this procedure which was not already obtained from better standardized techniques of activation. Hence, it was concluded that CPZ in the dosage used was of no significant value in this series of patients.

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DIAGNOSTIC ÉLECTRO-SOUS-CORTICO-GRAPHIQUE DE LA MORT DU SYSTÈME NERVEUX CENTRAL AU COURS DE CERTAINS COMAS

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INTRODUCTION

Les méthodes actuelles de réanimation, en particulier l'utilisation de prothèses respiratoires (appareil d'Engström), permettent de suppléer aux arrêts respiratoires survenant chez certains blessés crâniens.

Dans certains cas, ces syncopes respiratoires peuvent être reversibles et des cas de guérison ont ainsi été rapportés (Wertheimer, Thèse de Jeunet 1957).

Dans d'autres cas cependant, malgré la respiration artificielle, aucune reprise de respiration spontanée ne s'annonce, comme cela fut le cas pour 4 malades dont nous allons résumer brièvement l'histoire pathologique.

OBSERVATIONS

Obs. 1: B... R..., sujet masculin de 23 ans, accident de scooter le 17.4.1958, coma immédiat (stade II), fracture du rocher droit. Le 18.4.1958 à minuit: crise comitiale généralisée suivie d'une apnée respiratoire. Trachéotomie immédiate. Reprise de la respiration spontanée qui reste cependant irrégulière, entrecoupée de pauses. A 5 heures du matin, nouvel arrêt respiratoire. Une respiration artificielle (méthode de Sylvester) est mise en jeu pendant une demi heure en attendant que soit branché l'appareil d'Engström; celui-ci est laissé en marche pendant 160 heures. Durant cette période sont pratiqués deux trous de trépan qui ne révèlent pas de collection sanguine.

Les explorations electriques ont lieu à la 80ème (fig. 1), 100ème heure. Exitus.

Obs. 2: R..., sujet masculin de 35 ans, accident de bicyclette le 1.5.58, coma immédiat (stade III), opéré au service d'urgence d'un hématome sous-dural aigu. Le lendemain pendant le transport au service neuro-chirurgical, syncope brusque. Respiration artificielle mise en jeu immédiatement, suivie de trachéotomie et mise sous Engström qui est laissé en marche pendant 50 heures.

Les enregistrements électriques ont eu lieu à la 24ème et 25ème heure. Exitus.

Obs. 3: M... G..., sujet féminin de 18 ans, renversée par une auto le 2.11.58, coma (stade II) immédiat. Les artériographies éliminent un hématome. Le 3.11.58 à 16 heures: apparition de pauses respiratoires, de courte durée (30 sec.), bientôt suivies d'une apnée; respiration artificielle pendant 5 min. (méthode de Sylvester) suivie de trachéotomie et de mise sous Engström. Deux trous de trépan sont pratiqués le lendemain matin et montrent un état de ramollissement de la matière cérébrale.

Les enregistrements électriques sont pratiqués à la 15ème et à la 18ème heure. Exitus (fig. 3).

Obs. 4: G... A..., sujet féminin de 53 ans, hypertendue; céphalées depuis Octobre 1958, suivies d'obnubilation et d'une crise comitiale généralisée. Foyer de souffrance pariéto-temporal droit à l'EEG. Le 7.11.58: intervention. Evacuation d'un hématome intra-cérébral temporal. A la fin de l'intervention, apparition de troubles respiratoires, apnée. Trachéotomie immédiate et mise sous Engström.

Enregistrement électrique à la 20ème et à la 24ème heure. Arrêt de l'Engström à la 28ème heure. Exitus (fig. 2).

Le tableau clinique de tous ces malades est identique. Il est fort caractéristique. C'est celui d'un mort qui conserverait un pouls bien frappé: l'immobilité est totale, les membres sont hypotoniques, aucun réflexe tendineux ou cutané ne peut être obtenu, les

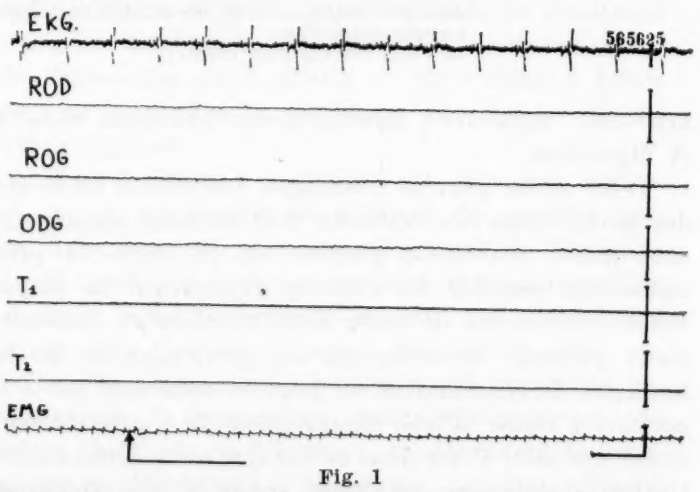

Fig. 1

Observation I — Engegistrement électrique pratiqué après 80 heures de respiration artificielle.

Absence d'activité électrique cérébrale, soit au niveau du scalp, soit au niveau des électrodes bipolaires introduites au niveau du thalamus (T1 - T2).

Persistance d'une très discrète activité EMG du muscle biceps droit.

Une stimulation nociceptive du membre supérieur droit (flèche) n'entraîne aucune réactivité EMG ou EEG.

Le cœur est régulier (EKG).

ROD - ROG : Rolando occipital droit et gauche.
ODG : Occipital droit et gauche.
T1 - T2 : Electrode profonde — Dérivation unipolaire.
T1 Electrode profonde — Dérivation bipolaire.

Calibrage 1 sec. 50 μV.

pupilles sont vitreuses, en mydriase et il n'y a aucun réflexe photomoteur. Toutes les stimulations, même les plus douloureuses, n'entraînent aucune réactivité ni motrice, ni cardio vasculaire. La température rectale marque dans sa courbe une chute lente traduisant la poïkilothermie relative. Cependant la peau reste colorée, et le pouls demeure bien frappé à un rythme inexorable (aux environs de 100/min.), tandis que la poitrine se soulève au rythme du respirateur artificiel. Persistent également les fonctions rénales et digestives.

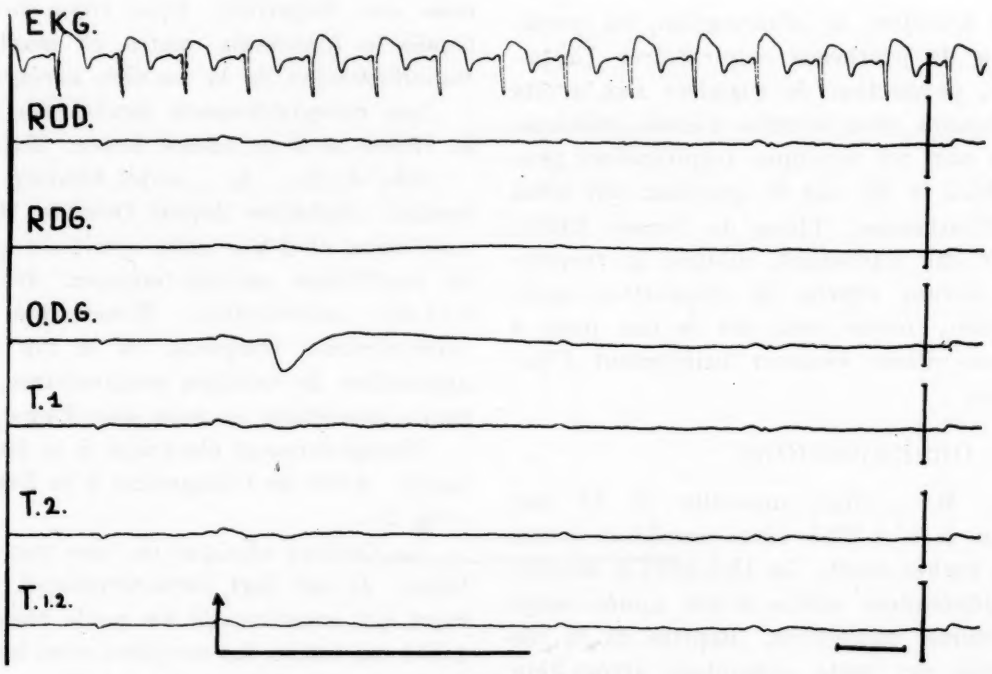

Fig. 2

Observation 4 — Enregistrement électrique après 24 heures de respiration artificielle. Absence totale d'activité électrique. Une stimulation douloureuse (flèche) n'entraîne aucune réactivité.
Le cœur est régulier (EKG).

Cette scène peut se prolonger des heures et même des jours. Chez ces sujets en état de mort apparente, *nous avons cherché à préciser de la façon la plus rigoureuse possible les critères objectivant la disparition irréversible de toute activité nerveuse centrale.* Nous pensons en effet qu'une prolongation de la tentative de réanimation *ne peut se concevoir que s'il persiste l'espoir d'une récupération de l'activité nerveuse centrale.* C'est dans ce but que nous avons étudié l'activité électrique cérébrale, index le plus fidèle et le plus sensible de la vie du système nerveux.

Activité cérébrale spontanée.

L'électroencéphalogramme enregistré au niveau du scalp (voir fig. 1-2) ne montre aucune activité électrique. L'absence totale d'artéfact musculaire est remarquable. Mais cette donnée ne peut être considérée comme suffisante: d'une part l'*activité électrique recueillie au niveau du scalp n'est qu'un lointain reflet des évènements corticaux* et il est possible que des variations de potentiels de faible amplitude au niveau de l'écorce ne puissent pas être détectées par nos appareils; d'autre part, l'observation animale enseigne qu'il peut persister une activité sous corticale, alors que le tracé cortical est muet, ce qui traduit la résistance plus grande à l'anoxie des structures sous-corticales. Aussi avons-nous exploré directement l'activité électrique diencéphalique, en introduisant de fines électrodes bipolaires stériles

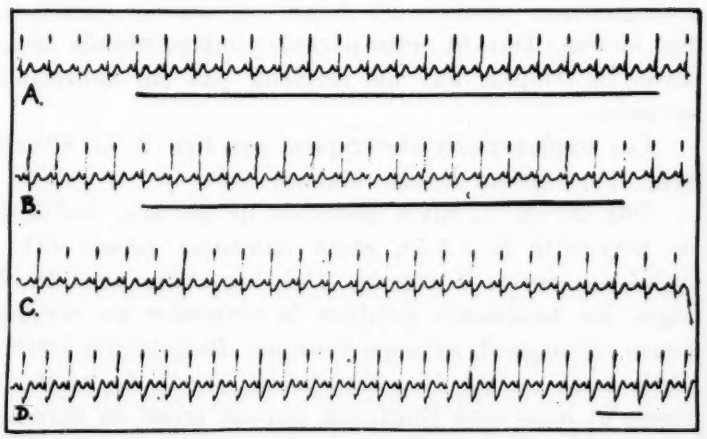

Fig. 3

Electrocardiogramme de la malade de l'observation 3, 18 heures après l'arrêt respiratoire:
A — Compression de la carotide primitive droite au cou,
B — Compression des deux globes oculaires,
C — Après injection intra-veineuse d'atropine,
D — Après injection intra-veineuse de d-amphétamine.

Noter l'absence de toute réactivité cardiaque au cours des trois premiers examens et l'accélération du système après injection de d'-amphétamine.

Le tracé EEG enregistré au même moment ne montre aucune activité électrique.

à travers les orifices de trépanation, en direction des structures médianes thalamiques. Aucune activité électrique n'a pu être recueillie. Cette exploration nous a permis également de constater l'état de ramollissement du cerveau, la matière cérébrale s'éliminant comme de la bouillie par l'orifice de trépanation.

Activité cérébrale évoquée

La stimulation électrique percutanée des troncs nerveux (sciatique poplité externe) ou la stimulation du thalamus chez ces malades, à différentes fréquences et à des voltages élevés n'a permis de recueillir aucune réponse évoquée au niveau du scalp.

De même, la stimulation intracérébrale, en allant de l'écorce à la ligne médiane à des voltages élevés (jusqu'à 140 V.), à des fréquences variables (de 1 à 60 c/sec.) et avec des ondes d'une durée de un à 10 msec., n'a entraîné aucune réponse motrice périphérique au niveau d'aucun territoire.

Ces trois ordres de faits permettent de conclure à la mort des formations diencéphalique et corticales, puisqu'ils témoignent de la disparition de toute activité « d'intégration », de conduction et d'automatisme.

Activité réflexe

Nous avons testé l'activité bulbaire de façon indirecte, en cherchant à agir sur la commande du système nerveux extrinsèque cardiaque: la compression des deux carotides au cou (réflexe sinocarotidien), la compression des globes oculaires (réflexes oculo-cardiaque) n'a entraîné aucune variation du rythme cardiaque (voir fig. 3).

De même, l'injection intra-veineuse de 1 à 2 mg. d'atropine n'a provoqué aucune accélération du rythme. Ces données permettent de penser que l'on se trouve chez ces malades devant *une véritable préparation cœur-poumon isolé,* le muscle cardiaque dont la résistance à l'anoxie est grande ayant échappé déjà au tonus cardio-modérateur d'origine bulbaire. Nous avons observé une seule fois une accélération du rythme de 90 à 108/min. par l'injection intra-veineuse de 100 mg. de Maxiton, que nous attribuons à une action directe sur le cœur.

Enfin, la réactivité des neurones respiratoires a été jugée par le test de l'arrêt de l'appareil d'Engström: aucun mouvement respiratoire ne se produit, même après une apnée prolongée. L'absence de mise en jeu des neurones respiratoires à leur stimulus le plus puissant, l'hypercapnie, traduit leur mort.

Il nous a semblé que l'ensemble de ces données négatives, recueillies chez ces sujets, à plusieurs reprises, à des intervalles de deux à trois heures permettait de poser avec certitude le diagnostic de mort « irréversible » du système nerveux central.

DISCUSSION

Ces observations soulèvent trois problèmes d'ordre différent:

1° Le premier problème est d'ordre diagnostic: il nous faut en effet pouvoir affirmer que l'activité nerveuse centrale a disparu de façon irréversible. La période de temps d'anoxie après laquelle des lésions *irréversibles* du système nerveux se constituent est difficile à préciser. Elle est variable en effet selon les auteurs et les structures envisagées. C'est ainsi que chez le chat, Sugar et Gerard (1938) constatent qu'une anoxie de 15 sec. entraîne une disparition totale de l'activité corticale, mais qu'il faut 4 min. pour que disparaisse l'activité électrique bulbaire. Il semble également que ce délai de 4 min. soit fatidique pour Ganshirt et coll. (1952), pour Kempinsky (1954), Meyer (1957) et Simpson (1934), une durée plus grande entraînant une disparition irréversible de toute activité nerveuse. Cependant, récemment, des arrêts de la circulation carotidienne et vertébrale respectivement de 11 et 7 min. ont pu être suivis d'une récupération fonctionnelle totale sur un sujet, il est vrai, en hypothermie selon Pourpre et coll. (1958).

On sait aussi qu'Heymans (1938) a pu constater chez le chien une résistance des mécanismes régulateurs bulbaires respiratoires et cardiaques à une anoxie de 30 min.

Enfin, H. Hermann dans la thèse de Sauzede (1942) rapporte même la récupération de réflexe bulbaire après un temps d'anoxie de 47 min. chez le lapin. Même en prolongeant ce délai de résistance à l'anoxie une heure ou deux, la constatation — à des intervalles de 3 heures — de l'absence totale d'activité électrique laisse donc une marge de sécurité suffisante.

2 Le deuxième problème est d'ordre pathogénique: le mécanisme de la mort du système nerveux, dans nos cas, relève certainement de l'anoxie; mais de nombreux facteurs ont certainement contribué à abaisser considérablement le seuil de réversibilité à l'agression anoxique. Dans la plupart des cas, en effet, la syncope respiratoire a été constatée immédiatement, la respiration artificielle mise en jeu aussitôt (méthode de Silvester), en attendant le branchement de l'appareil d'Engström, qui fut effectué dans le plus bref délai (cinq à 10 min.). Il semble donc que la période d'anoxie relative ait été brève. C'est pourquoi il faut incriminer non seulement des lésions anatomiques bulbaires (hémorragie dans le IV° ventricule, dans un cas, obs. 3) mais encore le retentissement à distance des lésions hémisphériques traumatiques de ces malades (foyer de contusion, de dilacération cérébrale, hypertension intracrânienne (Foster et Nims 1942)) responsables de désordres ischémiques et hypoxiques au niveau du tronc céré-

bral, comme le prouvent les travaux récents de Meyer (1957) ; selon cet auteur, des anoxies même brèves, tendent à diminuer considérablement le seuil de résistance des neurones respiratoires à une agression ultérieure, et il se peut que des troubles respiratoires prodromiques, passés inaperçus, aient aggravé considérablement, dans nos cas, une apnée même de courte durée. C'est donc en seconde et non en minutes que se compte le seuil d'irreversibilité anoxique sur un cerveau déjà lésé.

3° Le dernier problème enfin concerne l'arrêt de la respiration artificielle. Nous pensons que, si aucune reprise de la respiration spontanée n'est observée après 24 heures, se pose alors le problème de la survie du système nerveux central, condition nécessaire de la poursuite d'une réanimation. Un trou de trépan temporal bilatéral peut être réalisé qui permet l'exploration des structures profondes au moyen d'électrodes bipolaires; il permet souvent également de mettre en évidence l'état de ramollissement du cerveau.

L'absence de toute activité corticale et diencéphalique *vérifiée à plusieurs reprises* et à plusieurs heures d'intervalle, comme l'absence contrôlée de toute réactivité cardiaque aux différents stimuli, comme aussi une durée suffisante accordée à la réanimation (au minimum 24 heures) autoriseront la renonciation à la prolongation de toute thérapeutique.

RÉSUMÉ

La poursuite de tentatives de réanimation par respiration artificielle au cours de certains comas avec apnée prolongée ne semble légitime que si une récupération nerveuse est possible. Cette tentative semble devoir être abandonnée quand la mort du système nerveux central peut être établie de façon certaine. Pour affirmer ce diagnostic, nous proposons une étude poussée de l'activité électrique cérébrale recueillie non au niveau du scalp, mais par une électrode enfoncée par un trou de trépan dans les structures médianes thalamiques.

L'absence complète de toute activité d'intégration, de conduction ou d'automatisme au niveau du diencéphale, vérifiée à plusieurs reprises, permet d'affirmer la mort des formations diencéphaliques et corticales.

L'absence de toute réactivité cardiaque à des stimuli variés traduit la cessation de l'activité des centres bulbaires.

Ces conditions étant réunies, les chances de ces tentatives prolongées de réanimation respiratoire paraissent modestes, sinon nulles. Il est permis de se demander si ces garanties étant acquises, témoignant en faveur de la mort du système nerveux central, il est bien nécessaire de prolonger plus longtemps la respiration artificielle.

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PHOTOGENIC EPILEPTIC SEIZURES PROVOKED BY TELEVISION

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(Received for publication: January 10, 1959)

Lately, we have had opportunity to examine a boy, 12 years old, who presented epileptic seizures of the type petit mal since the end of 1957. The seizures were characterized by short absences, sometimes only by impossibility to speak. They did not cause distress of parents and for a long time were not treated.

About half a year later the boy had his first seizure of the grand mal type; he fell to the ground and the typical convulsions followed. Only then an antiepileptic therapy was started, during which the boy remained for 8 days without any seizures.

On the eighth day, the patient watched an evening television program for children. The picture, otherwise quite clear, blinked slightly. Shortly afterwards a typical grand mal seizure followed. A few days later, once more by watching the television, another similar seizure appeared.

An extreme sensibility to photic stimuli was testified by the fact that another seizure with unconsciousness and tonic-clonic convulsions appeared later when examining films against sharp morning sunlight.

The patient's family and personal history, just as the neurological findings, were completely negative. The boy is intelligent and does well at school.

Four EEG examinations altogether were made, the first three of which were negative. The fourth EEG registration made more than 6 months after the first seizure during television showed at hyperventilation a typical pattern of bilaterally synchronic spike and wave complexes. The activation by stroboscope, however, had a negative result. The reactibility to photic stimuli was perhaps already diminished in consequence of almost 6 months antiepileptic treatment.

Two reasons lead us to this brief communication:

(1) We have never met in literature with photogenic epileptic seizures provoked by television.

(2) In the time of mass spreading of television all over the world we must also bear in mind this possible photogenic provocation of epileptic seizures in our patients, especially in children.

Reference: KLAPETEK, J. Photogenic epileptic seizures provoked by television. *EEG Clin. Neurophysiol.*, **1959**, *11*: 809.

A STUDY OF THE USE OF RECORDED MUSIC IN THE ELECTROENCEPHALOGRAPHY LABORATORY

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(Received for publication: January 21, 1959)

The atmosphere of the laboratory and the handling of the patient are two of the most important aspects in obtaining a successful electroencephalogram. Experience has proven that the usual amount of anxiety and apprehension experienced by the subject necessitates a great deal of tact and understanding on the part of the technician to establish a feeling of comfort and relaxation. To assist the technician in his task, it was felt that the inclusion of music during the preparatory period and also during the actual recording would offer the technician a peripheral subject to serve as a supportive measure in the atmosphere of the laboratory. Familiar music tends to focus attention, and listening tends to keep the subject awake. Observations indicate that it is, generally speaking, a pleasurable experience and may effect some of the psychically painful effects of the procedure. It acts also as a blanket of sound to muffle out displeasing and alarming sounds. For some, the distracting affects offer another possibility in assisting the subject to relax enough to sleep. Certainly it serves to minimize the clinical aspects of the atmosphere. Primarily though, it establishes a common frame of reference to the technician and the patient through which communication can be initiated and a comfortable interpersonal relationship of a non-threatening nature created. Much more research is required to understand what roles music can play in the electroencephalography laboratory.

Reference: VEIT, H., MUSKATEVC, L. C. and MOLITOR, L. A study of the use of recorded music in the EEG laboratory. *EEG Clin. Neurophysiol.*, **1959**, *11*: 809.

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TECHNICAL NOTES

Edited by H. SHIPTON, A. M. BRIT, I.R.E. and F. BUCHTHAL, M.D.

A SIMPLE ELECTRODE SELECTOR SYSTEM

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(Received for publication: March 3, 1959)

Recent developments in depth electro-encephalography and polygraphic techniques have increased the number of electrodes many-fold, so that input selector switches must be very complex and expensive. A compact, simple inexpensive selector system has been devised and used in this Institute for some time and has proved versatile and trustworthy in operation, both for depth studies and for setting up any type of scalp electrode montage with polygraphic accessories.

The wires from the connectors leading to the implanted and scalp electrodes enter the selector box at the back and are terminated by miniature sockets, one for each electrode. *Each* input lead of the EEG differential amplifier is connected in the selector box to *two* miniature sockets of the same colour joined in parallel. By means of a length of flexible insulated wire carrying a miniature plug at each end, any one electrode socket, and thus electrode, can be connected to one input of an EEG channel. The other input of that channel can, by use of a similar plug lead, be connected to another electrode socket. If an electrode has to be common to more than one channel, connection is made from the electrode to say the "white" lead socket of ch. 1 and then, with another plug lead, from the socket which is in parallel with this "white" lead to say the "black" lead socket of ch. 2. Since there is a spare socket in parallel with this black socket, the same electrode can be connected to yet another channel and so on.

Figure 1 shows 3 channels connected bipolar fashion to 4 electrodes. As will be seen, there is *always* one spare socket which can be used for connecting the electrode to another channel.

If one electrode has to be connected to several channels, then there will be a number of plug and socket connections, but less trouble has arisen from the multiplicity of visible connections than from hidden faults in multiple connectors and switches and the inaccurate setting of rotary dials and sliders.

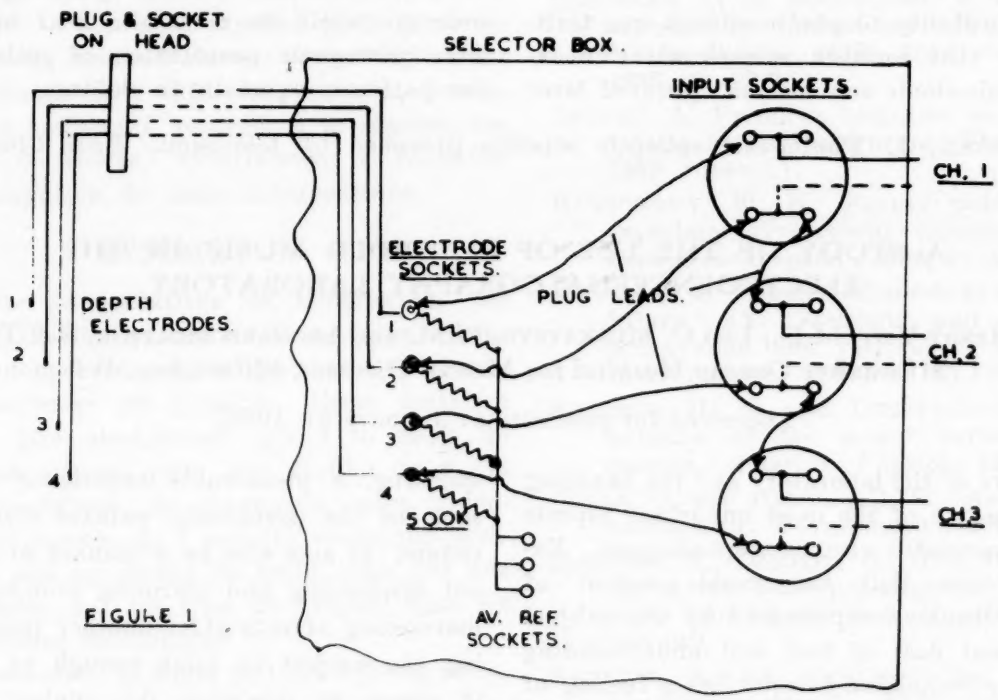

Fig. 1

Since the use of large numbers of electrodes permits accurate recording with respect to an average reference (Goldman 1950), 500 K resistors are permanently connected from each depth electrode socket to a common point to which several average reference sockets are connected (fig. 1). Thus, for recording with respect to average reference, the "white" input lead sockets of the EEG channels are all commoned and connected to the average reference point, and the

"black" lead connected to the required electrode socket.

Surface electrodes are connected to the same average reference point, but the value of the resistors is 270 K. This is done so that when the board is used for surface recording only (20 electrodes) the input resistance ($\frac{270}{20}$ K) of the amplifier connected to average reference is of the same order as that of the electrode resistance in the other lead.

67 through 73. The plugs and leads are brightly and distinctively coloured to facilitate tracing and checking of connections. A complete montage of 22 channels and 68 implanted electrodes can be set up in 5 min.

For convenience of numbering and to provide for possible increase of number of depth electrodes, the numbers are from 1-34 and 51-84 inclusive.

The box underneath is a separate attachment for polygraphic variables which can be connected by the

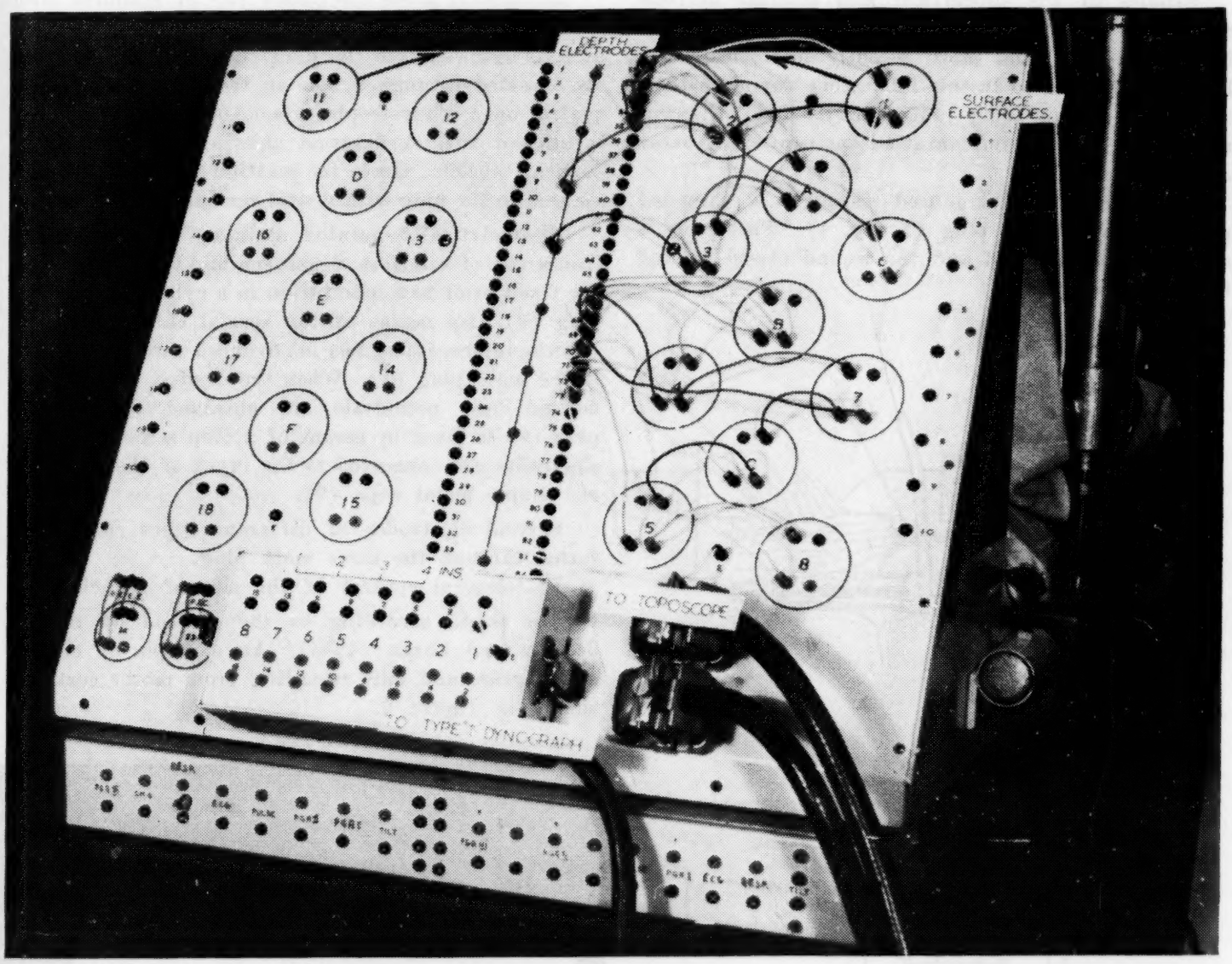

Fig. 2

Figure 2 shows a selector box which can be used to connect any of 68 depth and 20 surface electrodes to any of 22 toposcope channels and/or 8 channels of an Offner Type T Dynograph with provision for recording with respect to the average of all electrodes. Channels 1, 2, A, 3 and 6 are connected so as to record the voltages at electrodes 51, 52, 53, 54 and 55 with respect to the average reference. Channels B, 4, 7, C, 5 and 8 are connected bipolar fashion to electrodes plug leads to any of the recording channels. This unit contains the batteries and controls necessary for supplying transducers to record multiple PGR (potential and resistance), sphygmogram, EKG, EMG, pneumogram, speech and tilt-table inclination.

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A METHOD OF ELECTRODE IMPLANTATION IN UNRESTRAINED ANIMALS

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Studies of the subcortical and cortical nervous activity in unrestrained animals, primarily cats, with implanted gross, and more recently microelectrodes, have been conducted in this laboratory for more than 20 years (Kogan 1936, 1949, 1952). The following method of electrode implantation has proved the most advantageous.

Electrodes are introduced through a threaded plexiglass or ebonite plug (1, fig. 1). This plug is screwed into the skull and the wound closed around the neck marked 2.

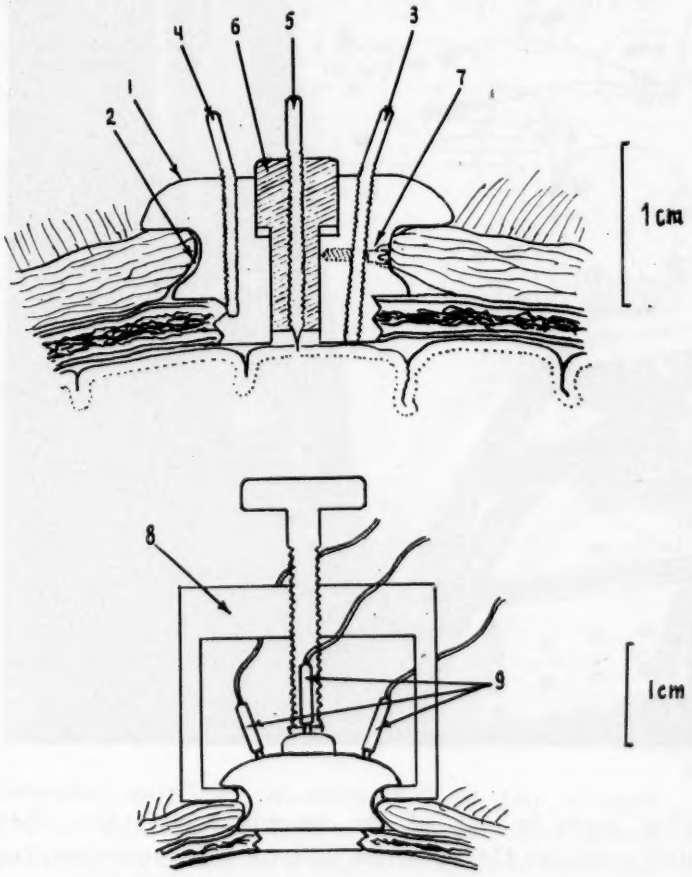

Fig. 1

Fig. 1

Diagram showing implantation of cortical gross and microelectrodes.
(1)plexiglass main plug, (2) neck of the plug, (3) extradural electrode, (4) electrode at bone, (5) microelectrode, (6) internal plug, (7) stop screw, (8) calibrated screw for manipulation of the internal plug holding the microelectrode, (9) caps with leading-off wires.

Extradural gross electrodes (3) of stainless steel including electrodes in contact with the bone (4) are directly screwed into the plug. Subcortical electrodes are inserted through a hole in the plug under visual control on a fluoroscopic screen, on which the X-ray is aligned with a diagram showing the major subcortical nuclei. Once in position the electrode is secured in the plug with dental cement.

Electrolytically pointed stainless steel microelectrodes (5) (Grundfest, Segstaken and Oettinger 1950) are fixed prior to implantation in a cylindrical ebonite plug (6). By means of the special calibrated screw (8) the internal plug (6) is advanced through a socket in the main plug (1). When the desired depth or the desired unit potentials are obtained the internal plug (6) is fixed by means of a stop screw (7). The electrodes are connected to the input of the amplifier via simple metal caps (9).

Several electrodes of different types can be inserted through the same main plug.

Histological control of the site of the electrode tips is made according to the method of Bishop, Jeremy and Lance (1953). An example of electrocorticogram and unit recording from motor cortex is shown in figure 2.

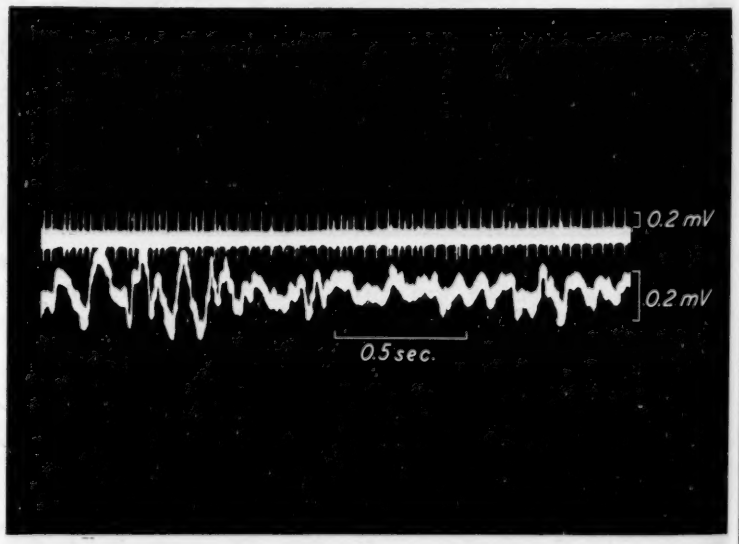

Fig. 2

Simultaneous microelectrode (upper trace) and gross electrode (lower trace) recordings. Microelectrode in fourth cell layer of motor cortex, gross electrode on the surface (cat).

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TIME DISTORTION IN ELECTROENCEPHALOGRAPH AMPLIFIERS [1]

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(Received for publication: December 15, 1958)

INTRODUCTION

Although much attention has been paid to various forms of distortion in amplifying systems in engineering literature, little has been written specifically in relation to distortion in electroencephalograph amplifiers. It is the purpose of this paper to draw attention to a distortion affecting the time axis, usually described as phase distortion, which can produce misleading stimulus-response times and the distortion of relation of components of complex patterns.

Phase distortion is an inherent property of any conventional amplifying system having a limited frequency response. In electroencephalograph amplifiers the attenuation of the lower and upper frequencies results in phase distortion at both ends of the frequency range. The effect of phase distortion on an artificial spike-wave pattern has been demonstrated by Geddes (1951). Dawson (1944) has shown low frequency filtering to distort the recorded form of a QRS complex, but little other experimental evidence of distortion affecting electrophysiological patterns has been found in current literature. The problem has been investigated further to demonstrate an important effect without enquiring deeply into its exact magnitude or mechanism.

METHODS

For the majority of experiments two adjacent channels of an electroencephalograph amplifier were used. The output feeding the pen of the first channel was suitably attentuated without distortion and fed into the input of the second channel (fig. 1a). Patterns from both amplifiers were recorded by appropriate pens and, knowing the pens produced negligible distortion (Saunders 1957), the distorting effect of the second amplifier could be determined by comparing the record of channel 2 with that of channel 1. In some experiments a cathode ray oscilloscope was used to measure the phase distortion of the amplifier.

RESULTS

The results of an experiment where a 3 c/sec. sine wave was fed into channel 1 and re-amplified by channel 2 are shown in figure 1b. The exact form of the signal feeding into channel 2 is represented by the recording of channel 1. It may be seen that the pattern of channel 2 has the appearance of occurring at

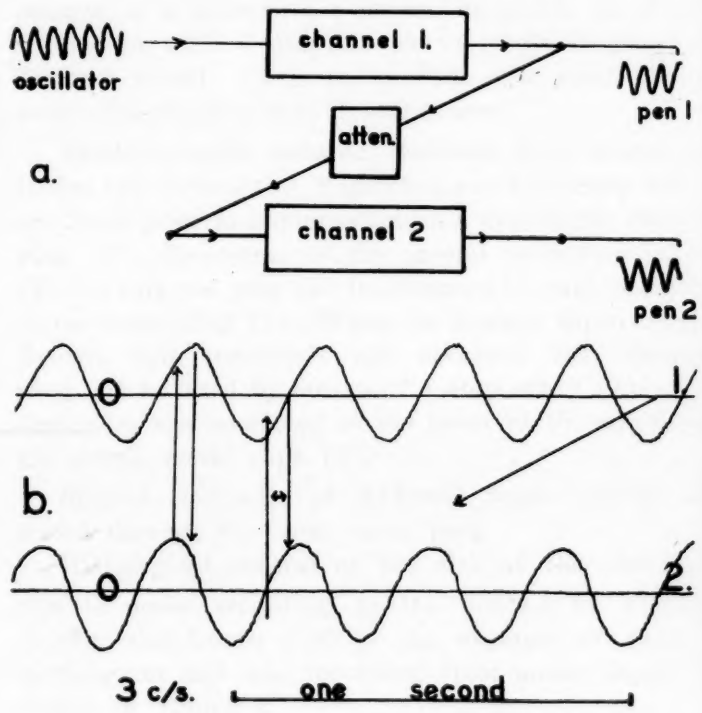

Fig. 1

a. The output of channel 1 is attenuated and fed through channel 2. The distorting effects of channel 2 are shown by comparing record 1 with record 2.
b. After amplification a 3 c/sec. signal appears to go through the phases of its cycle earlier than the signal feeding the input.

an advanced time to the pattern feeding its input. The 3 c/sec. sine wave of channel 2 crosses its baseline and reaches its maxima before the pattern of channel 1. With the higher frequencies it can be shown that the pattern of channel 2 lags behind that of channel 1. Using the technique of Lissajous' figures (Saunders 1957), it is possible to plot the degree of time advance or lag against the frequency of the signal feeding the amplifier (fig. 2).

To determine the cause of this apparent time distortion, the patterns of a sine wave as it was switched on were investigated. In figure 3a a sine wave was switched into the input of channel 1, the output of this channel fed into channel 2. It may be seen that channel 2 distorts the beginning phase of the pattern. In both, the signals leave the baseline at the same

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1 The observations described are part of a project of the Department of National Health and Welfare of Canada, Division of Mental Health.

The paper was presented at a joint meeting of the Central and Eastern EEG Societies, Toronto, Ont., September 1958.

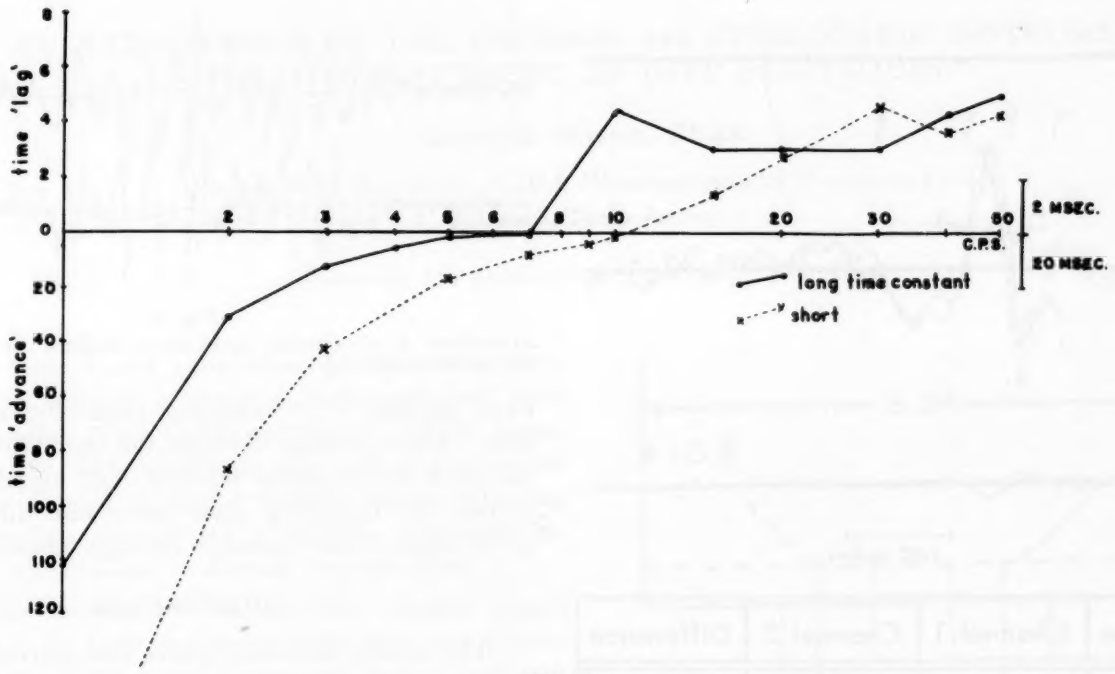


Fig. 2

The apparent advance or lag of sine waves of different frequencies produced by the amplifier.

instant. This preliminary distortion causes the subsequent sine wave to reach its zeros and crests several milliseconds before the sine wave feeding its input. If, in figure 3b, the point marked "S" were the indication of a stimulus, it becomes apparent that stimulus-response times may be distorted by passage through the amplifier. The interval from stimulus to the response as it first leaves the baseline is correct but thereafter timing to other components of the pattern is shortened. From figure 2 it may be seen that with the higher frequencies the opposite effect should occur, the amplifier causing patterns to appear later than they should do.

Stimulus-response times recorded from some electroencephalographic phenomena show similar effects to those described in the experiments above. In figure 4 a record of an eye-blink was made in channel 1 and re-amplified by channel 2. The records were cut out, oiled to make transparent and carefully superimposed

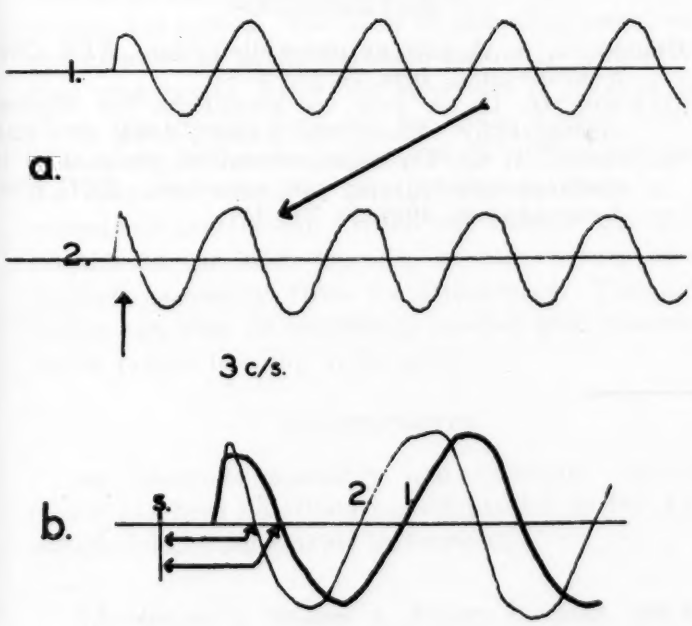
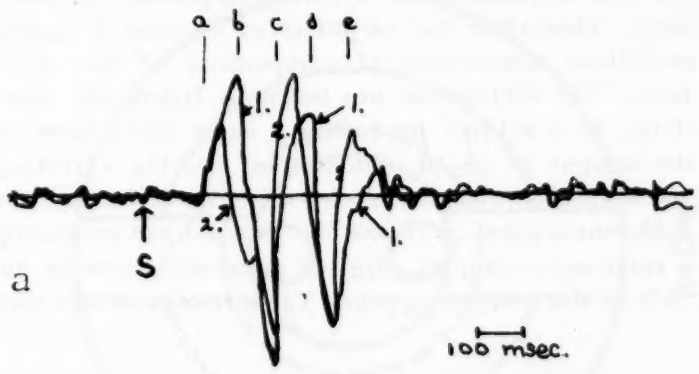


Fig. 3

The effect of the amplifier on a 3 c/sec. sine wave as it is turned on (**a**) from the original record, (**b**) the beginning of the above record enlarged and superimposed. "S" represents a theoretical stimulus mark.



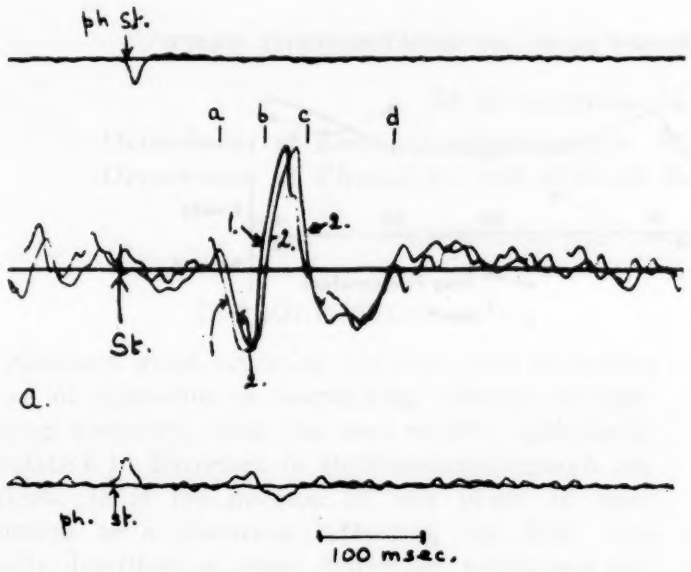
b.

Response	Channel 1	Channel 2	Difference
a	117 msec	117 msec	0 msec
b	216 "	183 "	-33 "
c	292 "	275 "	-17 "
d	366 "	350 "	-16 "
e	466 "	416 "	-50 "

Fig. 4

a. Eye blink potential recorded before and after passage through amplifier. Tracings superimposed to show distortion.

b. The change in stimulus-response times after passage through the amplifier.



b.

Response	Channel 1	Channel 2	Difference
a	100 msec	106 msec	+ 6 msec
b	137 "	143 "	+ 6 "
c	180 "	184 "	+ 4 "
d	264 "	264 "	0 "

Fig. 5

a. Spike response from occiput produced by photic stimulation. Records superimposed.
b. Stimulus-response time alteration.

to enable differences in the patterns to be measured. The subject was told to blink at the point "S" and the first response to the eye-blink appeared 117 msec. later. Thereafter the amplifier of channel 2 caused premature appearance of components of the wave form. The differences are listed in figure 4b. Similarly, in a subject producing a short spike form at the occiput to photic stimulation, the lag affecting the higher frequencies is shown in figure 5a and the differences listed in figure 5b. In a subject producing a spike-wave complex (fig. 6) some variations in details of the complex appear. The duration of the slow

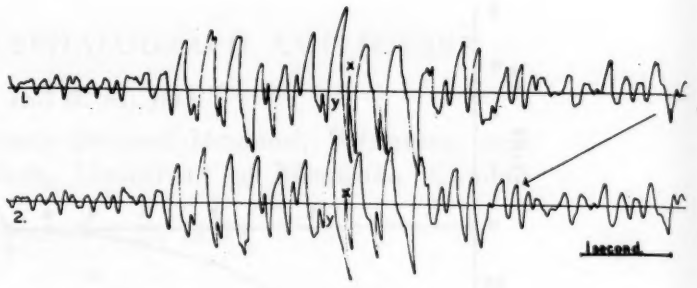


Fig. 6

Alteration of a complex spike-wave pattern by the amplifier. For details see text.

wave marked "y" changes from 200 msec. to 133 msec. after passage through the amplifier. Similarly, the peak of the spike marked "x" appears 75 msec. before the following slow wave but this is reduced to 63 msec. after passage through channel 2.

DISCUSSION

The results described above demonstrate the effects of phase distortion on stimulus-response times and of the timing of components of a complex wave form. These observations should be borne in mind when relating time to neurophysiological patterns. The clinical significance has not been investigated although it is evident that some complex patterns will be of different appearance when recorded by different machines having different time constants and high frequency filters. Similarly, it is possible that different equipment may give different stimulus-response times for identical phenomena. Finally, as modification of complex patterns can occur, false information may be sent into some types of frequency analyzers.

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AN ATTACHMENT TO THE JOHNSON 210 STEREOTAXIC INSTRUMENT FOR THE PLACEMENT OF DEEP ELECTRODES [1]

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(Received for publication: February 16, 1959)

It has been found convenient in this laboratory to fabricate bipolar electrodes from stainless steel surgical needles (fine intestinal needles, taper point, Torrington No. 721, length 44 mm). A nylon button (fig. 1) has been designed which, along with the surgical needles, constitutes a suitable electrode assembly for either acute or chronic implantation.

After the needles are cut to their proper length and soldered to their separate leads they are placed into the holes of the nylon button which are machined to allow a snug fit. The leads are then led out of the top of the button at right angles to the electrodes and into grooves provided in the button. A drop of dental cement [2] is put into the small cup provided in the top of the button. This cement adheres very well to the button and in addition provides good electrical insulation. After the electrodes are enameled and the tips exposed the electrodes are ready for use.

An attachment to the electrode carrier of the Johnson Model 210 stereotaxic instrument [3] has been designed which fits directly into the instrument and is held in place merely by tightening the thumb screw of the carrier (fig. 2). Rotation of the large knob on this attachment opens a set of jaws which are made to hold the button. The head of this attachment seats and clamps the nylon electrode button in perfect vertical alignment. After the electrode is lowered into place, the grooves exposing the nylon button may be utilized to anchor the button firmly to the skull while the electrode assembly is still held in place in the stereotaxic instrument. When the cement has dried, rotation of the knob provides an easy release of the electrode assembly from its attachment. The nylon button can then be completely covered with cement to insure proper bonding to the skull.

CONCLUSION

An electrode assembly and electrode orienting device has been described for adaptation to the Johnson Model 210 stereotaxic instrument.

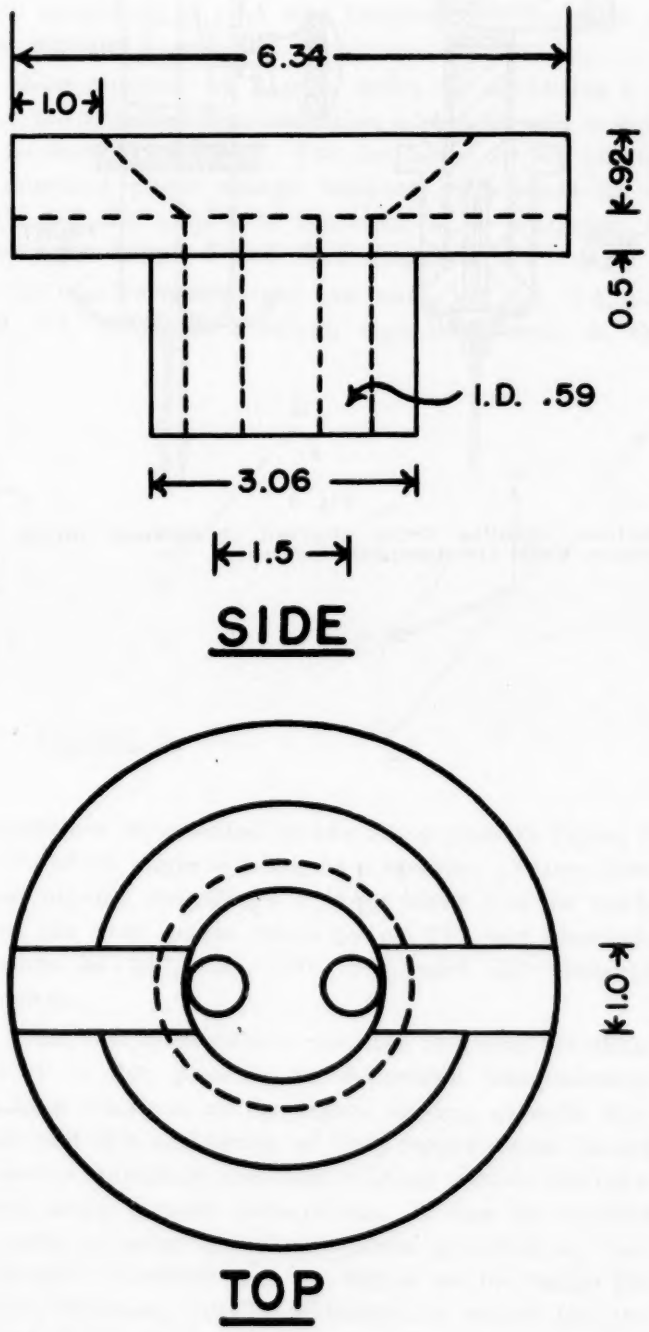


Fig. 1
Nylon button for electrode fabrication.

1 Fabricated by William A. Schaerr Company, 356 Gold Street, Brooklyn, New York.
2 Caulk grip cement, L. D. Caulk Company, Milford, Delaware.
3 Manufactured by C. H. Stoelting Company, Chicago, Illinois.

The author is grateful to Mr. Robert Moore of CIBA, Summit, for his many helpful comments and suggestions.

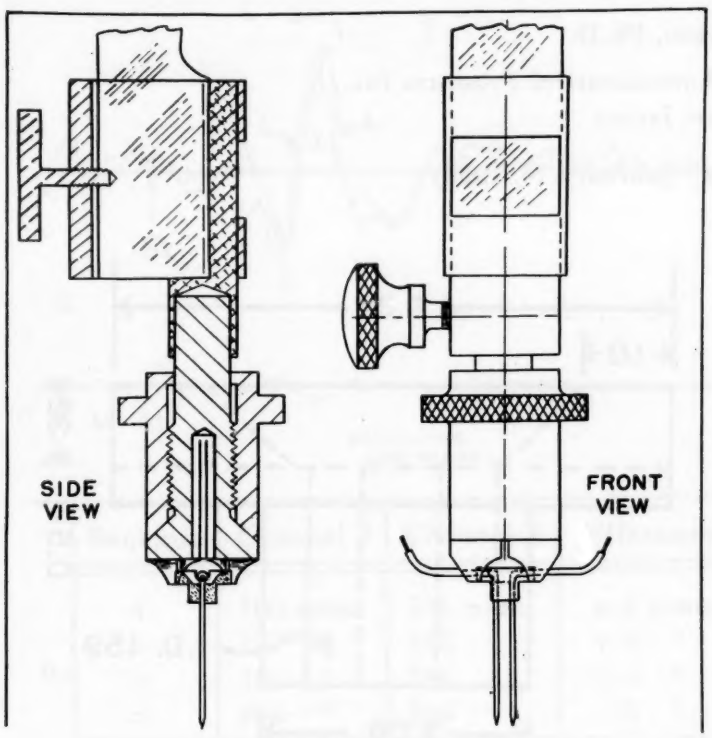
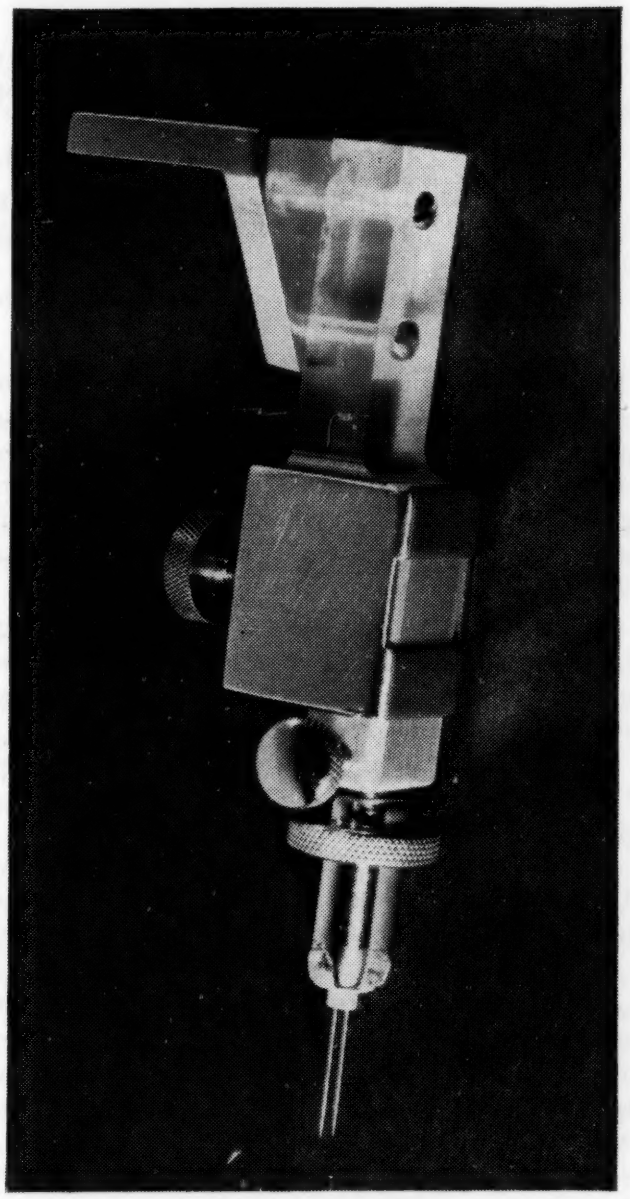


Fig. 2

Electrode orienting devise attached to electrode carrier of Johnson Model 210 stereotaxic instrument.



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AN AMBIGUITY OF BIPOLAR RECORDING

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The system of EEG recording generally referred to as bipolar derivation was introduced by Adrian and Matthews (1934) as a means for identifying a "focus". This is seen in conventional records as a phase difference of 180° between signals in two channels connected to three electrodes in line. In effect, this procedure is a differentiation of the potential differences with respect to space and the balanced push-pull input stages used for this purpose are correctly described as differential amplifiers. The appearance of a complete phase-reversal is undoubtedly the most delicate and easily visible indication of a gradient reversal and hence of a potential difference maximum, but this is the case only when the apparent equivalent generator within the head is effectively radial, symmetrical and stationary. In many conditions records taken with bipolar connection to a line of electrodes reveal phase differences other than 180°, and in such cases there is a real danger of mis-interpretation of the time differences since the system is liable to give ambiguous information for the following reasons.

Suppose that a line of electrodes is used for recording a single frequency signal which is small in amplitude at both ends of the line and larger in the middle (e.g. normal alpha rhythms in AP line over occiput), and that the phase of the signal is varying along the line of electrodes in such a way that the further along the line the later does the maximal amplitude of each wave occur, i.e. there is a progressive phase change from electrode to electrode, then bipolar derivations will exaggerate the time differences between channels.

The reason is best seen if the signals are represented as rotating vectors as is common practice in electrical engineering (Manley 1945). In this vectorial method the amplitude of the wave is represented by the length of the vector which is supposed to rotate in a clockwise direction with the frequency of the signal. Thus two signals A and B having the same frequency with differing amplitude, B being twice the amplitude of A, and having a phase difference of 40°, can be represented by two vectors as shown in figure 1 (a) and (b). In this case B is leading A.

If a balanced amplifier is connected one input to source A and the other to source B, the resulting signal is the vector addition of the two signals, remembering that one of the signals, say B, is reversed in phase by the connection to the amplifier (B'). This vector addition is shown as C in figure 1c and this is the signal seen at the output of the amplifier. The amplitude is 1.4A and frequency is the same as the signals A and B.

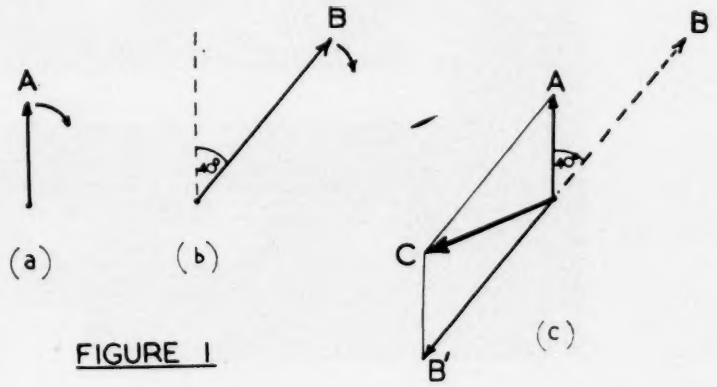

FIGURE 1

Now suppose we have a series of electrodes 1 - 7 and the vectorial representation of the signals in each is as shown in figure 2. For simplicity we will assume a constant phase change between each electrode of 20° and the amplitude increases to a maximum at electrodes 4 and 5 and then decreases.

If bipolar connections are made 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, then the resulting signals as seen at the outputs are represented by the heavy lines in figure 2. If the phase angle is taken as a measure of time from these bipolar recordings a large error will be made since the true phase relations of 20° per electrode appears as 18°, 18°, 80°, 80°, and 18° between channels.

From the information recorded in these six channels it is not possible to determine unequivocally the time relations of the signal arising at each electrode and this ambiguity of time measurement occurs whenever amplitude and time variant signals are compared using bipolar connections. It can be avoided by using unipolar recording system provided an "indifferent" electrode can be found or by using the Offner/Goldman (1950) technique in which the potential of an electrode is compared with the average of the potentials occurring at all electrodes. This latter system is to be preferred provided that the average remains about zero which is usually the case if more than twelve widely spaced electrodes are used and that there is no large common signal to all channels as in a diffuse spike-wave discharge.

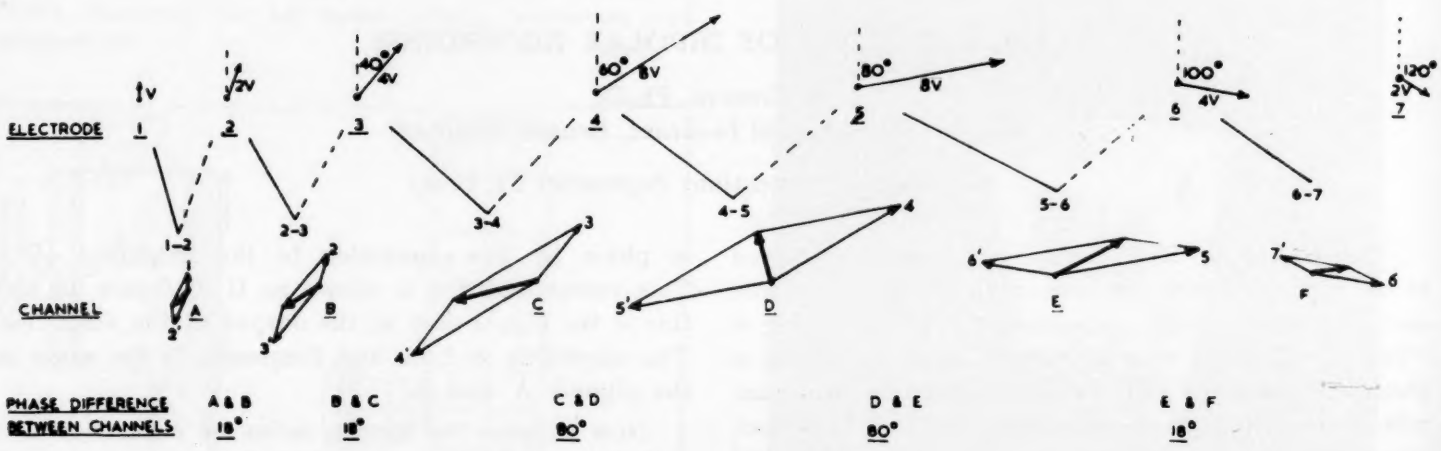

FIGURE 2

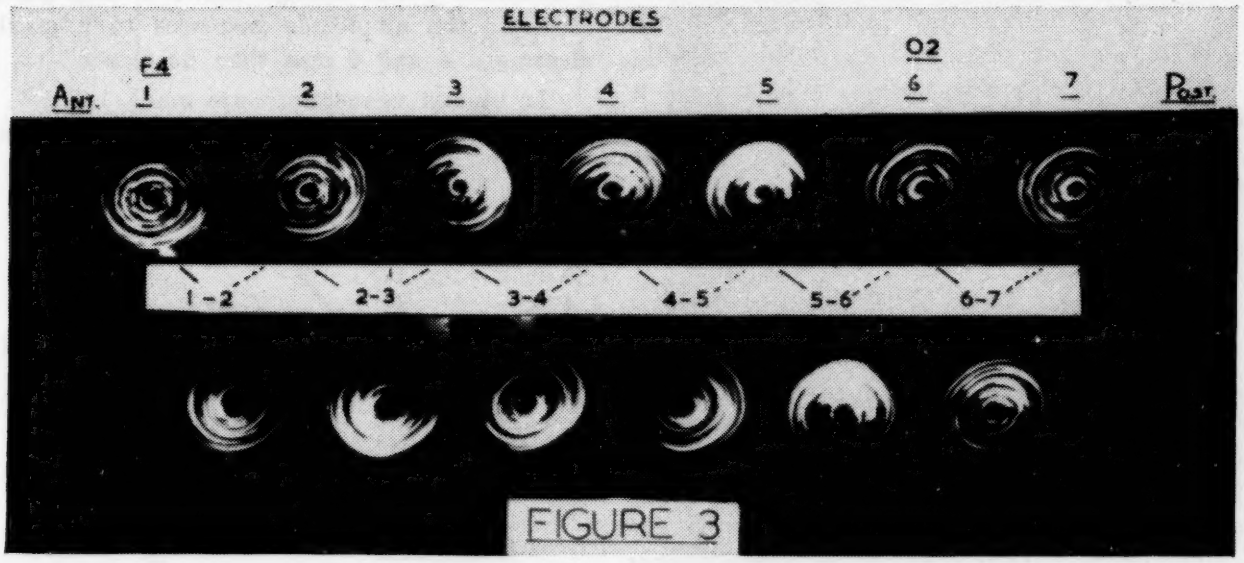

FIGURE 3

Figure 3 shows the differences that can occur in an actual recording of alpha rhythms. The records were taken from an AP line of electrodes on the right hemisphere of a normal male adult, using the Helical Scan Toposcope (Walter 1957) and show a progressive time delay from posterior to anterior region of the head. (The spot moves in a clockwise direction thus the signal at, say electrode 5, is reaching maximal amplitude earlier than the signal at electrode 4.)

The ''phase'' of the signal is given by the bright sector in each tube and the upper line shows the potential of each electrode against the average derived from 16 electrodes on the head (Goldman 1950). The lower line shows simultaneous bipolar derivations across the electrodes as indicated. The upper line which gives the true time relations between the alpha rhythm as recorded on the seven electrodes shows that apart from a large change between electrodes 1 and 2, there is a fairly constant time change of less than 2/12 of a revolution per electrode. The bipolar derivation on the lower line shows only a small time change between channels 1, 2 and 3, but a large time change amounting to half a revolution between channels 3 and 5 which could give time measures from these channels an inaccuracy factor of two or three.

Whenever possible, therefore, unipolar or average reference method of recording should be used for such time measurements and it should be mentioned that it is not necessary to have a large number of channels in order to use the average reference technique, but only a large number of electrodes connected to a common point through high resistances.

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ELECTRODES EN DAMIERS POUR ENREGISTREMENTS CORTICOGRAPHIQUES

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Le modèle d'électrodes présenté ici a été réalisé pour réduire le temps d'exploration corticographique au cours des interventions neurochirurgicales. En effet ces examens électro-physiologiques per-opératoires sont devenus au cours des dernières années moins fréquents pour de multiples raisons, les unes tenant aux indications elle-mêmes moins larges des exérèses chirurgicales dans les cas de foyer épileptique, les autres tenant sans doute à la difficultée d'établir pendant la courte exploration électrique des critères d'interprétation de l'activité recueillie après les exérèses; cette désaffection semble avoir été favorisée accessoirement par les complications qu'entraînent ces corticographies per-opératoires: matériel généralement encombrant, difficultées de fixation de l'appareillage, allongement du temps d'intervention ...

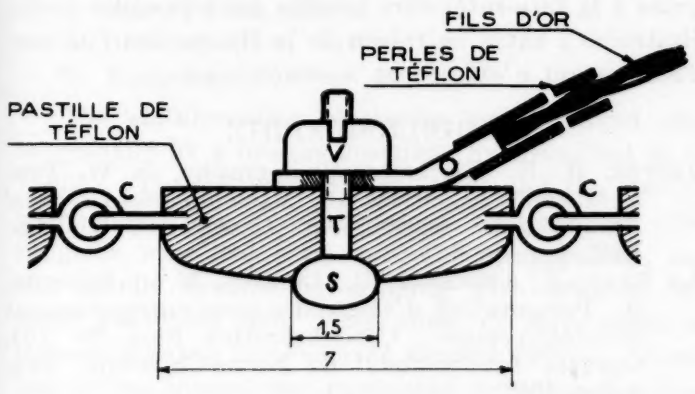

Fig. 1

Représentation d'une « pastille porte-électrode » montrant en grisé la pastille de polytétrafluoréthylène dans laquelle est insérée une sphère (S) d'argent soudée à un tube plein (T) d'or blanc sur lequel est fixé par une vis (V) un œillet amovible (O) sur lequel sont soudés les fils conducteurs en or fin. Les pastilles sont reliées entre elles par des chaînons (C) en platine.

Le damier est constitué par 16 électrodes d'argent disposées en 4 rangées reliées entre elles par des attaches souples qui maintiennent leur disposition géométrique.

Chaque électrode (fig. 1) est constituée par une sphère de 15/10 de mm. obtenue par fusion de fil d'argent de 6/10 de mm. de diamètre. Cette sphère est soudée à un tube plein d'or blanc, de 1 mm. de diamètre et de 2,5 mm. de longueur. Cet élément conducteur est maintenu par une pastille de polytétrafluoréthylène (Téflon) de 7 mm. de diamètre, de 2,5 mm. d'épaisseur dont il perfore le centre. Les « pastilles porte-électrodes » ont une face inférieure bombée. Chaque électrode (pastille et conducteur) pèse 0,64 grammes. Les 16 électrodes (fig. 2) sont articulées entre elles par des chaînettes de platine qui s'insèrent aux extrémités de deux diamètres perpendiculaires. La distance inter-électrode est de 11 mm. Le fil conducteur qui relie l'électrode à la boîte de connection est constitué par 4 brins de fil d'or de 1/10 de mm. tressés et protégés par une gaine discontinue de Téflon. Ce fil amovible s'insère sur l'électrode grâce à un petit œillet fendu en platine. Cet œillet est rendu solidaire de l'élément en or fin grâce à une vis en or fin. Afin d'éviter toute tension préjudiciable aux fils conducteurs qui sont fragiles, lors de manipulations, des chaînettes en platine un peu moins longues que les fils conducteurs ont été fixées sur 8 des « pastilles porte-électrodes »; quatre de ces chaînettes relient une rangée de « pastilles porte-électrodes » à la boîte de connection, les 4 autres relient la rangée symétrique à un petit bloc de Téflon identique à celui dans lequel est inséré la boîte de connection.

La boîte de connection comporte 16 fiches plus une 17ème destinée à recevoir le fil de terre qui se termine par une pince crocodile en platine. De la boîte de connection partent 16 fils protégés par une gaine de matière plastique qui se rendent à une fiche radio-air à 17 broches.

L'ensemble décrit est stérilisable dans un appareil de Poupinel et supporte facilement des températures supérieures à 150°C. La boîte de connection et l'élément analogue sur lequel s'insèrent les chaînettes qui supportent le damier des 16 électrodes, permettent d'ailleurs le stockage de cette mosaïque: elles viennent s'insérer dans une boîte spéciale sur 2 supports disposés de telle sorte que les électrodes restent suspendues sans toucher les parois de la boîte.

Comme on le voit, ce dispositif convient particulièrement à l'enregistrement cortical de surface (Le Beau 1957); c'est-à-dire qu'il ne saurait remplacer dans toutes leurs indications d'autres appareils qui permettent d'atteindre en particulier des structures d'un abord moins aisé (face interne des hémisphères,

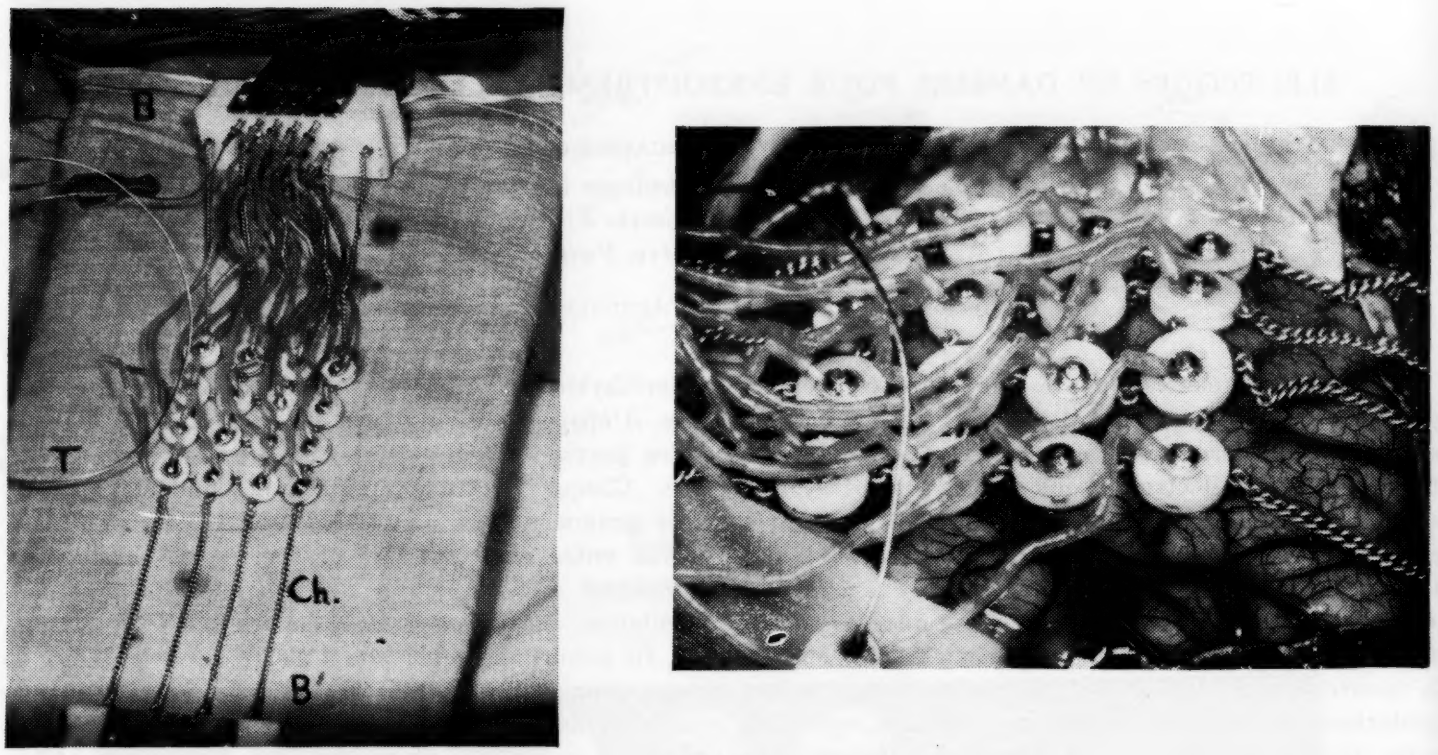

Fig. 2
A gauche, se trouve la photographie du damier de 16 électrodes posés sur un champ opératoire, on voit les chaînettes (Ch) qui relient le damier à la boîte de connection (B) et à un bloc de Téflon (B′) ; en T fil de terre.
A droite, se trouve la photographie du damier en place sur le cortex montrant comment le damier épouse le relief des circonvolutions.

sillons, structures sous corticales ...)[1] cependant, les avantages en sont multiples; en effet:

1° le temps de pose sur le cortex est très raccourci du fait de la mise en place simultanée de la totalité des électrodes;

2° le matériel aisément stérilisable, nécessaire à l'enregistrement est réduit;

3° la répartition géométrique permet une exploration systématique avec un repérage plus aisé et surtout de nouvelles explorations avec la même disposition en cas d'enregistrements per-opératoires successifs;

4° le contact électrode-cortex est assuré directement sans l'intermédiaire de conducteurs;

5° les mouvements éventuels survenant sous une électrode, soulèvent celle-ci et son support sans glissement ni modification de pression ce qui évite les artefacts;

6° la souplesse de l'ensemble permet un bon contact de toutes les électrodes; elle est obtenue par une liaison souple non élastique des électrodes entre elles, grâce à la face inférieure bombée des « pastilles porte-électrodes » enfin en raison de la finesse des fils conducteurs qui n'effectuent aucun travail.

1 Tels que ceux couramment utilisés de Grass (Schwab 1951) ou de Jasper (1948). De très nombreuses électrodes uniques ou multiples ont été imaginées pour l'atteinte des structures profondes: Meyers (1948) Walker (1948), Walter (1946) en ont, parmi les premiers, réalisé des prototypes.

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THE EROSION OF ELECTRODES BY SMALL CURRENTS

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(Received for publication: March 23, 1959)

Stainless steel electrodes have often been used to stimulate or to produce lesions in the central nervous system. Direct current is generally used to produce lesions and it is sometimes employed in stimulation, although it is more common to stimulate by means of alternating currents. Experiments in this laboratory involving the production of electrolytic lesions led to the discovery by one of us (H.W.) that the tips of electrodes used in the destruction of tissue were being seriously eroded. It appeared desirable, therefore, to investigate such changes more systematically, and to extend the investigation to cover electrode changes produced by alternating currents used for stimulation.

ELECTRODE MATERIALS

1. Malin & Co. "Wilstabrite Stainless" soft dental ligature, .010".
2. Hoskins Mfg. Co. Chromel A, .010".
3. Platinum alloy: 90 per cent platinum, 10 per cent iridium, .010".
4. Sterling silver, .010".
5. Tungsten, .005".

The stainless-alloy electrodes were pointed electrolytically by a process described by Grundfest *et al.* (1950). The platinum-iridium alloy and the sterling silver electrodes were sharpened by grinding. The tungsten wire had been enameled commercially, and was merely beveled by clipping with scissors. All other electrodes were given three or more coats of General Electric Co. Formvar Enamel (9825). (Beading of the enamel was minimized by using a motor-driven retractor to withdraw the electrodes from the enamel bath very slowly.) Electrodes pointed electrolytically are so sharp that the enamel shrinks away from the tips. The tips of the silver and platinum-iridium electrodes were cleaned by brushing them gently with a fine stone.

EROSION FROM ALTERNATING CURRENTS

In figure 1, electrodes 2 to 6, inclusive, show tip erosions that developed with amplitudes and durations of alternating currents within the range of values common to our conditioning experiments. The procedure for classical conditioning, employed in our laboratory, is to give an animal 20 training trials per day (Loucks 1959). In many of our experiments the conditioned stimulus consists of two trains of AC impulses administered directly to the brain through implanted electrodes. Each train is approximately .5 sec. in duration, the two being separated by an interval of .5 sec. The cumulative AC stimulation for a one-hour training session would thus total 20 sec. Over a 30-day training period — the duration of many experiments — the subject would receive 600 double-train stimuli, or 10 min. of AC stimulation.

Most of the examples of erosion shown in figure 1 were produced by passing current between electrodes immersed in physiological saline. It should be noted, however, that no. 5 (stainless steel) is one electrode of a pair implanted in the occipital region of the brain of an experimental animal used in a conditioning experiment. The training extended over a period of 18 days. During this time the electrodes were used to administer 303 AC conditioned stimuli to the brain, at a rate, commonly, of 20 per day. For the first 11 days of training the current varied between .6 mA. and 1.4 mA., the median value being 1.2 mA. During the last week of training the currents ranged from .20 to .26 mA., with a median value of .24 mA.

Electrode no. 6 (stainless steel) is one of a pair inserted into the brain of an anesthetized animal. A total of 800 double-train AC impulses with an amplitude of 2 mA. was administered at the rate of 1 every 9 sec. The cumulative period of AC stimulation was 13.3 min. It is evident from these two examples that very serious electrode erosion can be produced in vivo, just as in vitro. A current of only .1 mA. AC passed through saline for a total time of 3.3 min. (one double-train of impulses every 9 sec.) produces an erosion of a pointed stainless steel electrode that is very apparent when the tip is examined under the microscope.

Current passed between the tips of tungsten electrodes immersed in physiological saline results in the mushroom-like accretions characteristic of stainless steel electrodes. Sterling silver electrodes, immersed in saline, seem to become slightly cupped by the passage of a 2 mA. current for a cumulative time of 3.3 min.

In contrast to the erosion produced in electrodes made of stainless steel, tungsten, or sterling silver, platinum-iridium electrodes seem to be unaffected by comparable magnitudes of alternating currents. A

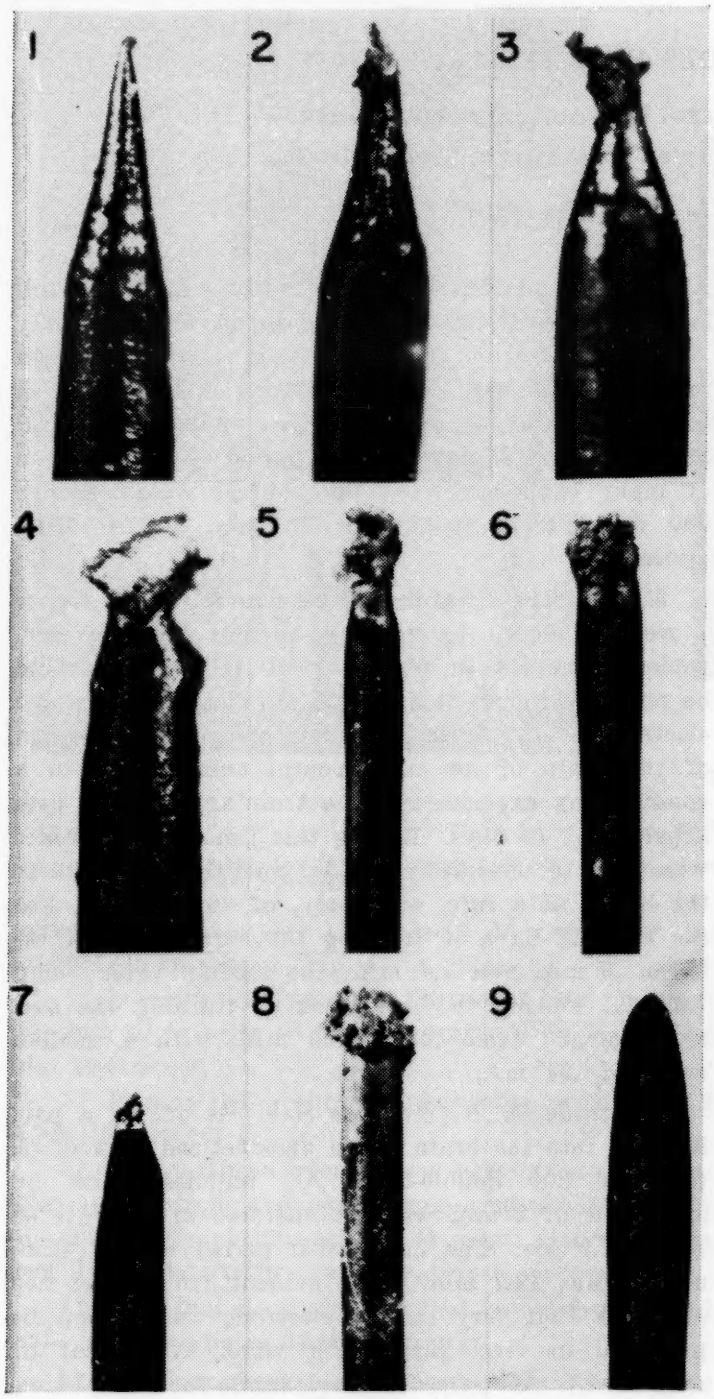

Fig. 1

Illustrations of electrodes and tip erosions.

All electrodes are .010" in diameter but were photographed with different magnifications. Electrodes 1 through 7, inclusive, are made of Malin & Co. "Wilstabrite Stainless" soft dental ligature wire. All these electrodes were initially pointed electrolytically. Electrode no. 8 is of sterling silver, and no. 9 is made of an alloy containing 90 per cent platinum and 10 per cent iridium. These last two electrodes were initially tapered by grinding. All electrodes were insulated to the tips by three coats of General Electric Co. no. 9825 Formvar enamel, baked according to specifications.

Electrode no. 1 (stainless), unused: the bend at the extreme tip was produced inadvertently during photography.

Electrode no. 2 (stainless) is one of a pair subjected to a current of .3 mA. 200 c/sec. AC for a total time of 3.3 min. immersed in physiological saline. The current consisted of a series of two .5 sec. AC trains of impulses given at the rate of one double-train secquence every 9 sec.

Electrode no. 3 (stainless) is one of a pair subjected to a current of .5 mA. 200 c/sec. AC for a total time of 3.3 min. while immersed in physiological saline. The rate of giving trains of impulses is the same as that for electrode 2.

pair of platinum-iridium electrodes imbedded in the brain of an anesthetized animal was subjected to a current of 2 mA. for a cumulative time of 17.3 min. All stimuli were administered during one experimental period at a rate of one double-train series of AC impulses every 9 sec. No sign of erosion could be detected when the electrodes were examined under a microscope.

EROSION FROM DIRECT CURRENTS

In producing electrolytic lesions in the central nervous system, it is a somewhat common practice to implant a stainless steel electrode with a stereotaxic instrument. This electrode is then used as anode in conjunction with a cathode of large surface area applied to the skin. A direct current of 2 mA. passed for 20 sec. is often employed to produce an electrolytic lesion. Electrodes 7 (stainless), 8 (sterling silver), and 9 (platinum-iridium) were subjected to DC while immersed in physiological saline. A commercially enameled tungsten electrode, .005", beveled by clipping, was also used as an anode in physiological saline while subjected to 2 mA. for 60 sec. It developed a cup-shaped erosion similar to that of the stainless steel electrode, no. 7, but the opacity of the enamel prevented the eroded cavity from showing in a photograph, and it is not included in figure 1. In contrast to the erosion produced in the stainless steel and sterling silver electrodes by direct current, the platinum-iridium electrode showed no sign of erosion that could be detected under a microscope.

The pattern of erosion caused by DC differs from that due to AC. When AC is passed between a pair of stainless steel electrodes immersed in saline, accretions build up at each tip and ultimately form

Electrode no. 4 (stainless) is one of a pair subjected to a current of 2 mA. 200 c/sec. AC for a total time of 3.3 min. while immersed in physiological saline. The rate of giving trains of impulses is the same as that for electrode 2.

Electrode no. 5 (stainless) is one of a pair implanted in the occipital region of the brain of an experimental animal used in a conditioning experiment. The training extended over a period of 18 days. The electrodes were used to administer 303, 200 c/sec. AC stimuli to the brain at a rate, commonly, of 20 in each daily training period. Over the first 11 days the median current was 1.2 mA.; during the last week the median current was .24 mA.

Electrode no. 6 (stainless) is one of a pair subjected to a current of 2 mA. 200 c/sec. AC for a total time of 13.3 min. while implanted in the brain of an anesthetized animal. The rate of passing successive trains of impulses is the same as that used with no. 2.

Electrode no. 7 (stainless) is the anode of a pair of electrodes subjected to a DC of 2 mA. for 60 sec. while immersed in physiological saline. The removal of metallic material from the tip of the electrode has proceeded until the end consists of a shell of translucent insulation, plugged with a clump of granular material.

Electrode no. 8 (sterling silver) is the anode of a pair of electrodes subjected to a DC of 1.7 mA. for 60 sec. while immersed in physiological saline.

Electrode no. 9 (platinum-iridium alloy) is the anode of a pair of electrodes subjected to a DC of 2 mA. for 60 sec. while in physiological saline.

mushroom-like deposits extending out from the edge of the enamel. The deposits are somewhat granular and are easily dislodged from the edge of the enamel insulation. The passage of DC through a stainless steel anode immersed in saline produces a relatively clean cavity within the confines of the enamel insulation. A similar type of cup-shaped erosion develops within the insulation of the tungsten anode. In contrast, a sterling silver anode develops a mushroom-like accretion, similar to those formed in stainless steel and tungsten electrodes by the passage of AC.

SIGNIFICANCE OF ELECTRODE EROSION FOR STIMULATION OR DESTRUCTION OF TISSUE

Inasmuch as the excitatory or destructive effectiveness of current applied to living tissue is related to current density, it is evident that the population of cells affected by eroding electrodes will vary as the contours of the exposed tips are modified. When an anode, subject to erosion, is used to produce a series of electrolytic lesions, the volume and contour of the successive lesions might vary even though the amplitude and duration of the DC were carefully controlled. The effective current passing area of an eroding anode is likely to exhibit irregular variations as it is implanted at successive positions, due to the accumulation and disloging of deposits at the tip. Even when stainless steel electrodes, chronically implanted, remain rigidly fixed in position, the formation of deposits at the tips must progressively alter the configuration of cellular excitation.

SIGNIFICANCE OF ELECTRODE EROSION FOR IMPEDANCE CHANGES

It has been a standard procedure in our studies of conditioning, using implanted electrodes, to monitor the impedance of the tissue circuit between the electrodes. It was our hope that we could detect tissue changes at the tips of the imbedded electrodes, where current density would be greatest, from changes in the electrode-tissue impedance. The AC used in stimulation is stabilized by a "constant current" amplifier described by Guttmann (1957), and its amplitude is monitored by taking readings from a vacuum tube voltmeter placed across a resistance in series with the electrodes. The impedance of the electrode-tissue circuit is estimated by using a cathode-ray oscilloscope, placed directly across the stimulating electrodes, to register the amplitude and waveform of the AC impulses. The equivalent impedance of the electrode-tissue circuit, in ohms, can be ascertained by substituting a known resistance giving an equivalent amplitude of deflection on the oscilloscope.

With a fixed value of stimulating current the electrode-tissue circuit exhibited such erratic fluctuations of impedance that an effort was made to take systematic measurements of the impedance of stainless steel electrodes while immersed in a sealed test tube of physiological saline. It was found, however, that the electrode-saline impedance also varied most erratically. Some of the changes could be attributed to polarization effects, which with audio frequencies can be very appreciable. Thus, it might not be unexpected that the impedance would vary with the size of the current. For example, a value of 5,000 ohms was obtained with a current of .4 mA. whereas an impedance of approximately 10,000 ohms developed with 1.2 mA. Similarly, changes in impedance with the duration of the current or with the number of spaced repetitions of successive currents at any one experimental period might be ascribed to polarization. It was difficult, however, to account for the very marked variation in electrode-saline impedance from day to day when measurements were taken with a fixed amplitude of current at comparable points in a series of daily measurements. On one day, for example, the initial impedance was approximately 10,000 ohms. The following day it was 15,000 ohms. Furthermore, the changes in impedance were not always in one direction. Progressive increments in the impedance of electrodes imbedded in living tissue might be ascribed to the formation of scar tissue, but the variation of the saline impedances were so erratic as to appear almost lawless.

Upon the discovery of the extensive erosion and the accretions at the tips of the stainless steel electrodes, a plausible hypothesis presented itself to account for fluctuations in impedance. Mechanical dislodgment of the deposits at the tips of stainless steel electrodes might well account for erratic variations in impedance. The validity of this hypothesis is suggested by the fact that the impedance of platinum-iridium electrodes, which do not develop accretions, has shown a variation of less than 5 per cent over a period of many weeks. This degree of stability in the impedance of the electrode-saline circuit suggests that if changes of a significantly higher order of magnitude develop with a long term stimulation of living tissue, the increase might prove to be diagnostic of cellular changes, e.g., growth of scar tissue in the region of the electrodes.

CONCLUSIONS

The implications of our observations are unmistakable. Electrodes made of stainless steel alloys and of tungsten which have only small areas of exposed metal are not suitable for studies in which it is important to stimulate a particular population of

neural elements consistently. When such electrodes are used for the electrolytic destruction of tissue, the results are likely to be more variable than when platinum-iridium electrodes are employed. Platinum-iridium electrodes will maintain the most constant tip contour because of their chemical inertness. It is conceivable that some of the variations in the results from stimulation or electrolytic destruction of nervous tissue, frequently noted in previous experimentation, may be due to the erosion of the electrodes used to administer the currents.

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AUTOMATIC ANALYSIS OF THE ELECTROENCEPHALOGRAM: A REVIEW AND CLASSIFICATION OF SYSTEMS [1]

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Automatic analysis of the EEG carries a certain magic. The complex patterns generated from moment to moment have always given promise of understanding just beyond measure. This shadow of magic has inspired the construction of machines to answer questions about brain waves which may not be meaningful in terms of brain function. Since the significant factors in the EEG are still questionable, a reasonable analytical procedure has seemed to be one which retained all information in the original wave. However safe this criterion might at first appear, it defeats the very purpose of analysis which is to abstract and emphasize only significant changes. A reversible transform (Preston 1954), allowing exact reconstruction of the signal from analyzed data, may be mathematically sufficient but not meaningful for EEG analysis in that it may make interpretation even more difficult than before.

As long as neurophysiological coding remains unknown and mathematical criteria appropriate to the EEG have not been established, information can be extracted from the EEG wave only on a "best guess" basis. The designer must furnish the automatic analyzer with a series of questions to be asked of the EEG signal; these questions are usually influenced by the special interests of the designer and therefore reflect clinical experience, neurophysiological theory and the current state of the art in analyzing equipment. However, certain constraints are set by the EEG as an amplitude-time distribution, since the questions can only be asked about a fixed time interval and answered as amplitude variables, or asked about fixed amplitude relationships and answered as variables in time. If the determinant or fixed coding unit is a standard interval such as a cycle of frequency, the resultant or variable unit is measured in terms of amplitude or energy and the analysis is said to be in the frequency domain. If the fixed coding unit is a given or standard amplitude relation, such as selected voltage levels, peaks or base line cross of the waves, the variable is measured in terms of real time and the analysis is said to be in the time domain. The convenience of the above consideration is that it establishes the major classifications into which all attempts at automatic analysis of the EEG seem to fall. The basic functions of any system may be understood as operating principally in either the time domain of fixed amplitude relations or in the frequency domain of variable amplitude relations, but almost always at the cost of information not completely resolved in the other domain.

The time resolution of the system must be considered at two stages in the analytical process. The time required for the equipment to treat a basic unit of information in the EEG is the limiting factor in its degree of resolution. A high resolution system should therefore code its information in such a way that the basic unit is shorter than the time required for significant neurophysiological changes. What this time interval may be will depend on the neurophysiological process under analysis. The second consideration of time in any practical system is the interval required for display and data analysis. While data analysis itself may be reasonably delayed in many instances, data display must again be consistent with significant neurophysiological time intervals.

Resolution in time should be distinguished from the power of the system to resolve useful information. The mosaic of cortical activity may more readily give up information to a multiple area display or to a proper long term averaging of single channel data than to the most refined and elegant of the microscopic techniques. As will be seen, all of these considerations have played some part in automatic analysis.

1. ANALYSIS IN THE FREQUENCY DOMAIN

Inherent in the concept of frequency is the assumption of periodicity, the periodic recurrence of identical wave forms. A standard amplitude distribution called the sine wave is further assumed as the shape of the amplitude as it changes with time in a single cycle. Since frequency is the rate of repetition of these cycles, a given frequency is sufficient to establish the qualitative class for analysis. Knowing the class, characterization proceeds by designating the quantitative unit, amplitude.

Many complex wave shapes can be characterized as the sum of regular sine waves by the use of the Fourier series (Carslaw 1930) which accounts for phase,

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amplitude and frequency [1]. Application of this powerful technique has been limited since the required calculations are extremely laborious. Early attempts were made by Dietsch (1932), using this analysis, but so little data can be processed in this way that physiological correlation is impractical. This process of Fourier analysis is often offered as the theoretical basis for "harmonic" analysis. However, a clear distinction must be made between Fourier analysis and the partial approximation rendered by the limited terms available from a relatively few, phase insensitive filters. Filter analysis takes many forms but depends on recurrence or repetition to sort out the qualitative units. This process leads to theoretical limitations which have been seen as analogous to Heisenberg's uncertainty principle Licklider (1951) in that frequency filters must leave "uncertain" time relations. This uncertainty is due only in part to the inherent time lag which degrades the resolution of transient changes. After filtering, display of amplitude or energy most conveniently takes the form of integration. In most of the following applications integration is simply the summation of the area under the curve, where the curve may be any signal such as the primary EEG trace or the sine wave output of a resonant filter. Since circuits operate on definite integrals, the integration must have limits or a start and stop time. The time over which integration is accomplished differs with the various systems and the purpose for which they are designed. Instrumentation for automatic frequency analysis has been an adventure in the state of electronic art, and has usually forced a compromise between high resolution and rapid processing of data.

A. *High Resolution Processing*

Endless loop systems in which a sample of EEG record is literally made into a closed loop for indefinite replay lend themselves to high resolution analysis. This allows a single variable filter to repeatedly survey the record for a given frequency. An optical apparatus was used in the original application of this technique to EEG by Grass and Gibbs (1938). Photo-electric reduction of 30-sec. strips of record showed considerable difference between epileptic and normal frequency spectra (Gibbs 1941). An improved model of this analyzer with a one cycle resolution was built but the increased resolution offered disappointingly little additional information. Extensive experience with frequency analysis encouraged Grass and Gibbs to this classic criticism: "Much experimentation with the data finally leads to the conclusion that, although frequency analysis has advantages for revealing certain general features of the EEG, it is not satisfactory for clinical purposes. No index, either simple or complex, based on one or on many spectra from a given case, can express the highly specific detailed information contained in the EEG" (Gibbs 1947). Various other optical systems have been suggested (Dawson 1953; Furth 1944), but none have been shown to be practical for large scale EEG data reduction.

Endless loop systems are well suited to magnetic tape and drum recordings. Power spectrum analysis (Barnes 1953) of 3 min. EEG samples on magnetic tape show sensitivity to changes in the state of consciousness and suggest that the deeper the sleep, the closer the power spectrum approaches white noise. In this analysis, automatic circuits square the frequency spectrum to yield the power spectrum, an operation reminiscent of Glesser's square-root transformation (Glesser 1954) applied in order to smooth frequency analyzer data. Crosscorrelation and autocorrelation, as used by Brazier and Barlow are endless loop systems; actual computation is carried out on a digital correlator (Brazier 1952) or with magnetic drum delay (Barlow 1954; Brazier 1956). While correlation techniques are sensitive to phase and have no limitations on frequency components represented they must see a relatively long EEG sample. Barlow (1957) has modified the correlator developed at M.I.T., by replacing the multiplier with a gating and storage circuit that allows amplitude sampling at fixed delay times after the stimulus. Such modification circumvents the longer EEG sample required for autocorrelation and results in an analysis similar to the Dawson technique to be described below. As in all endless loop systems there is the problem of rapid data processing, but these techniques are extremely powerful in handling rhythmic evoked responses and the area distribution of a particular component. Correlators may be seen as a special class of filter which indicates recurrence or repetition of an amplitude point in successively longer fixed time intervals and tends to emphasize information about the longest or fundamental period, at the expense of smaller oscillations (Dawson 1953).

Photographic overlay methods have been developed by Bates (1951) and Dawson (1951) which allow extremely high resolution but only over short periods. Here again is a filtering action with amplitude repetition in a fixed time interval abstracted and emphasized. This method seems most useful for single stimulus response since the interval is automatically established by the physiological constants of the evoked potential. Dawson has also extended the principle of the overlay method to an electro-mechanical averager, which samples and stores successive time slices of the signal amplitude. For the last several years he has been working on an all electronic device using a spe-

1 Fourier himself was not able to prove this relationship or to establish which complex waves the sine series could characterize (D'Abro 1951).

cially constructed cathode ray tube for storage and display. The technical difficulties to be overcome in the development of this latest system appear to be formidable.

B. *Continuous Processing*

The problem of continuously analyzing at a rate comparable to EEG generation has been met most successfully by a series of high ''Q'' tuned filters, such as in the Walter analyzer (Baldock 1946). It would be redundant to describe the Walter analyzer but it should be mentioned that active work still continues in an effort to improve the filters (Shipton 1956) integrators (Ulett *et al.* 1954) and data standardization (Yeager 1955). The delta band is particularly sensitive to artifact and is often disregarded in practice. The most difficult and frustrating practical problem in working with frequency spectra is the treatment of the analyzed data. This problem has been rendered by Knott (1953): ''For the most part, the data from wave analyzer investigations have been treated subjectively. This is to be deplored, for an instrument designed to complement *visual* analysis should not lead just to further visual analysis.'' Despite the very real disadvantages and difficulties met in general application of the resonant filter analyzer, excellent basic research has been accomplished by a number of investigators, particularly relating personality structure in populations to the analyzed EEG as in the work of Ulett (1953) Kennard (1955; 1957) Mundy-Castle (1953) and Walter (Cooper *et al.* 1957).

The theoretical limitations of this system have not been resolved but several modified approaches have tried to improve over high ''Q'' filter characteristics. Heterodyne (beat frequency) scanning instruments have been developed by Barbour (1947) and Drohocki (1951) but standardization for clinical application has not been reported. In an attempt to shorten time constants to one-half second and increase detail in the time domain, a series of 20 low ''Q'' filters feeding directly into a twenty cathode ray oscilloscope display was developed by Markey *et al.* (1949). Data was recorded on 35 mm. film; the problem of subsequent data reduction must have been enormous, and use of this system has been limited. Bekkering *et al.* (1956) have developed a series of filters which display their outputs as lines of a width proportional to intensity. Since the outputs are visualized one on top of the other they give the appearance of a ''spectogram''. This device can be used with magnetic tape recordings of the EEG and has allowed the interesting collaboration of Van Leeuwen in Holland with Gastaut (1957) in France in current topographical studies. Kozhevnikov (1956) in Leningrad has also developed a system of band pass filters which have a comparatively large band width and therefore high time resolution. Display in this system employs integrators which may be fed into numerical counters. An additional piece of apparatus analyzes the duration of the fluctuations being measured to emphasize small ''deviations in frequency''.

Perhaps the most direct continuous processing method in the frequency domain is the integrator of Drohocki (1956) which has a minimum time resolution of 1/400 of a second and displays the summed amplitudes of the primary trace as a proportional number of simple spikes per unit time. A similar device has been used by Forbes *et al.* (1956) when he applied the integrator circuits of Bickford's servo-anesthesia mechanism (Bickford 1951) to the study of barbiturate effects in cats. He presents an interesting comparison of the integrator readout with ''brain wave count'' manually analyzed. The specialized application of Bickford's method to anesthesia requires band passing the EEG through an 8 c/sec. filter before integration. A similar method for measurement of per cent alpha time has been instrumented by Morris (1956) using an 8 to 13 c/sec. filter. Shagass' (1957) excellent work on barbiturate threshold in psychiatric patients also uses this type transform in the Ulett integrator (Ulett and Loeffel 1954).

C. *Special Applications*

Frequency analysis finds most useful application in systems developed for the study of limited and special problems.

The ''comb filter'' (Brazier *et al.* 1952) was developed by Casby specifically for analysis of rhythmic evoked potentials and area spread. Garceau (1954) was interested only in a measure of the delta index and its relation to schizophrenia in his automatic integrator circuits. Itokawa *et al.* (1952) combined delta integrating circuits and beta filter circuits to measure depth of anesthesia in both the ether and barbiturate groups. A time-gated amplitude quantizer (TGAQ) (Putter 1954) has been specifically designed for analysis of data obtained in electrophysiological experiments with acoustic stimuli. This equipment gives a digital readout of the amplitude difference between two manually fixed points in time, usually set to begin automatically at the expected peak of the evoked potential and set to end at the following peak.

D. *Interval Point Coding*

For practical computation the continuously varying voltage of the EEG signal may be converted to finite digital form by point sampling. A theorem in information theory, called the ''folding phenomenon'' (Shannon 1949), specifies the minimum number of points to be taken to give complete information. If equidistant points are taken at a rate $(2 + 1)$ times the highest frequency present, all information is retained.

Assuming 30 c/sec. to be the highest significant EEG frequency, 61 samples per sec. must be taken. This relation establishes a ''confidence level'' for automatic amplitude sampling of 60 per sec. such as used by Remond and Offner (1952). Their method was designed to show spatial relations of several channels as a plot of potential spread across the scalp and results in a topographic display of potential gradient. More recently Remond (1956) has modified the original analyzer with storage circuits that sample the amplitude in a fixed time interval after a sensory stimulus. Semi-automatic data reduction with curve followers such as a ''Telereader'' write out on IBM cards contain complete information but no clue as to necessary computation or display. Multiple factor analysis has been undertaken on data in this form by Kris (1953) to classify EEGs by ''vector score on each axis''. In response to a U. S. Air Force request, a General Electric research team (1954) proposed use of a special automatic factor analysis computer to determine the most significant variables in the EEG.

Interval point coding allows analysis in both the frequency and time domain, depending on the computation carried out on the sampled points.

2. ANALYSIS IN THE TIME DOMAIN

Systems of analysis which abstract and emphasize particular amplitude points or their relationships as they vary in real time are said to be in the time domain. Since the central problem in this type of analysis is selection of the significant amplitude points for coding, the nature of central nervous system coding and the neurophysiologically significant changes in the EEG are even more critical than in frequency analysis. The following systems are classified according to the amplitude points emphasized; the variable unit to be measured is the time of occurrence of these selected points.

A. *Peak Point Coding*

Statistical treatment of the primary trace by Sato (1952) has taken peak amplitude points as the significant population and suggested that this EEG population shows the predictable behavior of a stochastic process. Shaw and Roth (1955) have recently used the positions of maximum positive and maximum negative points in a normalized signal to determine position of the generating dipole in their electrical field model of EEG activity. The dramatic Walter Toposcope (Walter *et al.* 1951) is an analog amplitude display over multiple areas with the peak points always emphasized as the brightest spots. The amplitudes of a given EEG signal are presented in their time relation to two variables: (*a*) the synchronizing sweep which may be an oscillator input, another EEG signal or a repetitive stimulus such as photic flicker; (*b*) to EEG peak points displayed from all other areas. The sweep rate on each small oscilloscope is determined by the synchronizing signal. If a peak point in the analyzed signal occurs once within the full cycle or sweep time of the synchronizing signal, one bright line or ''petal'' will appear on the scope face. The displacement of the line from 12 o'clock indicates the time position of the analyzed peak point within the full cycle of the synchronizing wave. Since the peak points of all analyzed signals are related to the single synchronizing signal, their phase or time relation to one another is displayed. Of course, if two or more analyzed peak points occur within the sweep time, two or more bright lines will appear, indicating that harmonics or multiples of the sweep frequency are present in the analyzed signal. This type of peak amplitude display in 22 channels presents a major data processing problem since the patterns must be photographed and measured for quantitative analysis. The difficulty of even visual interpretation of these patterns has been colorfully set forth by Grey Walter himself. ''Frequency, phase and time relations of the rhythms are shown in what at first appears to be a completely bewildering variety of patterns in each tube and in their ensemble'' (Walter 1953).

The toposcope carries information about wave amplitudes a bit before and after the peak point. Thus, both clock position and petal spread read out amplitude relationships, even though absolute amplitude is largely disregarded; as Walter explains, since the eye is unable to make accurate estimations of brightness change, the method is not well adapted to the measurement of signal amplitude (Walter *et al.* 1951). Recognizing the limitations imposed by photographic integration of this display, Shipton (1957) has improved the original circular scan by introducing a helical scan circuit which causes the CRT beam to progressively spiral outward.

Perhaps the least complicated of popular systems have been those which continuously read out amplitude changes as intensity of display. This analogue display of a continuous signal makes a fairly simple system with no intervening operations of analysis and has encouraged use of multiple channels in an area pattern corresponding to the recording electrodes, such as has been developed by Cohn (1942) and Goldman *et al.* (1948), but most widely applied by Lilly (1952). In the system devised by Lilly, 25 amplified signals are fed into neon lights whose intensity is proportional to absolute positive-negative amplitude. Unfortunately, amplitude-intensity displays are as tedious and difficult to quantitate as the potential maps of the neurophysiologist which they resemble. Use of high speed photography (128 frames per sec.) increases resolution but also increases the amount of data to be processed. Application of this type of analysis

seems to be most productive when limited to very small active areas such as one sq. cm. of the acoustic cortex. Under these conditions, the forms and figures of cortical activity can be visualized on a surface. This type of intensity-time display has limited advantage over classical amplitude-time display in a comparable number of channels. Tunturi (1954) describes a 60 tube cathode ray oscilloscope array photographed with a 4 x 5 in. aircraft camera which allows detailed electrical maps of the cortex to be plotted from the visualized amplitude trace. The problem of data processing sounds familiar as Tunturi puts it: ''Thus, one of our major problems that we are struggling with now is that of data measurement and reduction''.

A more sophisticated automatic analysis of amplitude distribution has been suggested by Lonsdale (1952). Circuits measure the width of successive waves at several preselected amplitude levels to give the sum of the time, t, for which the function was equal to or greater than the selected amplitude. A ratio of t over the total time of the sample, T, is taken for the various amplitudes. The time ratio t/T at, say, the 5 V. level is plotted and then added to t'/T for the 6 V. level which is plotted and then added... This computation results in a cumulative distribution curve which statistically characterizes the total population of waves. Increased resolution results from treating the first and second derivatives of the original signal in the same way. Experimental results show different ogive (cumulative distribution) curves for various mixed sine frequencies. This system was also designed for ''random functions'' and application to EEG has been considered. Another characterization which should prove profitable in EEG is the amplitude-distribution density, one of the important statistical properties of a signal. An amplitude-distribution analyzer (King 1951) has been constructed for signal components from dc to 1000 c/sec. This distribution density is related to the Lonsdale ogive in that it is the derivative of the cumulative distribution function, or the relative probability that the signal amplitude lies within a narrow range of amplitudes centered about the level x as:

$$P(x) = \text{Probability}\ [x < f(t) < x\,dx]$$

B. *Baseline Cross Coding*

While absolute amplitude and frequency influence visual interpretation, probably the dominant factor in ''retinocortical'' (Dawson 1953) analysis is the phase-amplitude-frequency complex of wave shape. The most easily delineated aspect of wave shape is period or duration at certain amplitude points such as the base line. Manual attempts at quantitation by measuring or counting wave periods extend throughout the history of EEG, and the term index has become almost synonymous with measurement of wave lengths or periods (half-wavelengths). The alpha index (Davis *et al.* 1936) and delta index (Hoagland *et al.* 1936) as the number of these waves per second or as percentage time occupied by these waves are both averaging devices of rich heritage. The real need for a simple method of determining frequency spectrums led Engel (1944) to plot the population of one second samples in a length of record. The samples were characterized by a simple count of the number of waves in the one second sample. This method has been criticized by Kaufman and Hoagland (1946) who prefer the method of Brazier and Finesinger (1944) which sums the periods of each ''frequency'' in a 2 min. record and derives a plot of total time percentage occupied by wave lengths of a given period.

Period measurements have been the most practical of all manual reductions and with such an empirical background it might be expected that automatic systems coded by base line cross would have been popular. Surprisingly few systems have been developed which use the EEG base line cross as the command signal and information unit, although a noise analyzer has been developed which measures the probability distribution of the zero-crossing intervals in a signal (Young 1954). Prast and Noell (1949) developed a base line cross analyzer as an anoxia warning device to produce a command signal indicating ''danger'' on the occurrence of a train of 3-4 waves in the 5-7 c/sec. range. This emphasis on a train of waves offers one of the few examples of analysis coded as to sequence. Stein, Goodwin and Garvin (1949) constructed a brain wave correlator which produces a square wave of the same sign as the original EEG signal, ''and which passes from negative to positive or from positive to negative at the same instant the original signal does. This square wave is independent of the amplitude and wave form of the brain's signal. When two trains of such square waves produced from signals originating in two different areas of the brain are fed into a proper detector, the result is a voltage proportional to the coefficient of correlation between the signs of the voltages originating in the two areas.'' This instrument can be modified to serve as a type of frequency analyzer which reads out the number of periods per second in a single channel.

The term ''correlator'' should not be confused with the mathematical process of crosscorrelation; in much the same way, systems designed for phase analysis may superficially appear to be in the frequency domain. However, phase analysis is in fact a comparison of relative amplitudes between two signals. It is clear that the variable is time itself in this sort of comparison. Phase analysis has enjoyed recent popularity in its use by Bagchi (1957) with photo-

graphic overlay techniques and Walsh (1956) using resonant chokes. Darrow (1956) has probably done the most extensive instrumentation on phase analysis with half wave rectification of signals fed into push pull amplifiers. He has simplified the data reduction by the use of a DC recorder which automatically writes out in-phase, out-of-phase differences. Topographical changes of the phase relationship can be demonstrated with change in the state of consciousness (Darrow *et al.* 1957).

C. *Wave Shape Coding*

The final system to be considered is a recent development which attempts to abstract wave shape information from the EEG as an aperiodic function. The theoretical rationale (Saltzberg *et al.* 1957) and description of the system are to be presented elsewhere, but the empirical approach can be seen as time domain analysis. Automatic period analysis of the EEG (Burch *et al.* 1955) utilizes the base line cross to establish each period as the basic unit of information which in turn is used to gate additional information. Each half wave period may be written out and is referred to as the *major period.* Wave shape is analyzed as the time relationship between points of inflection and the base line cross of the primary EEG. The first and second mathematical derivatives of the primary trace yield the time position of inflection points as the second derivative zero points. The time between these points is written out as the *minor period* and represents each superimposed "wiggle" on the primary trace. The superimposed frequencies, as well as the dominant or fundamental rhythm may be characterized as count per second (reciprocal of frequency) and the sum of minor periods per second (wave shape coding). The continuously processed data is readily converted to digital form so that numerical values can be obtained to emphasize such factors as wave symmetry, peakedness and phase.

Period analysis of half-wave resolution is accomplished by stable, relatively simple instrumentation that employs pulse width selection techniques rather than filters and is compatible with both high resolution writeouts and averaging over long epochs. A "new" device, it incorporates many of the suggestions and methods worked out by generations of electroencephalographic experience.

SUMMARY

A systems review of EEG analysis has been undertaken for both automatic instrumentation and semiquantitative manual reductions. It is proposed that EEG analysis can be classified into two logical categories according to the fixed unit of information coding designed into the system. Automatic period analysis of EEG wave shape is described as the most recent development in time domain analysis.

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SOCIETY PROCEEDINGS

SCANDINAVIAN EEG SOCIETY

Inauguration Meeting, September 13-14, 1958

Sahlgrenska Sjukhuset

Gothenburg, Sweden

Chairman: K. G. I. PETERSÉN

Secretary: C. W. SEM-JACOBSEN

Gaustad Sykehus, Oslo, Norway

1. Inauguration. — T. RÉMOND, Paris, France.

2. Conditioning reflexes in human and animal. — W. STORM VAN LEEUWEN *et al.*, Leiden, Holland.

3. Principles of central regulation of sensory input. — K.-E. HAGBARTH, Uppsala, Sweden.

From time to time it has been suggested that descending systems may terminate in centers of pure sensory character and thus control the synaptic transmission of sensory messages in the C.N.S. Succeeding a review of the previous data which support this suggestion, the following experiments on curarized cats were described (Hagbarth and Fex 1959). Spinal sensory tracts and the dorsal horns of the spinal gray matter were explored with a micropipette. Units responding to natural peripheral stimuli were identified and attempts were then made to modify the activity of these units by electrical stimulation of various stations in the brain (vermis, brain stem, sensory-motor cortex). The results indicate that postsynaptic sensory elements in the spinal cord are exposed to excitatory as well as inhibitory influences from the brain. It is argued that ''spontaneous activity'' in postsynaptic sensory neurones may be maintained not only by sensory inflow but also by tonic cerebral outflow. Additional findings suggest that this cerebral outflow may in turn be affected by sensory inflow.

4. The effect of the psychological significance of stimuli on evoked potentials in the human EEG and the startle reaction. — L.-E. LARSSON, Stockholm, Sweden.

An investigation has been made of the effect of the psychological significance of auditory and peripheral nerve stimuli on various types of evoked potentials in the human EEG and the startle blink reaction under different experimental conditions. It was assumed that stimuli given when the subject's attention is distracted have a low significance, stimuli given when the subject is passive have a moderate degree of significance and stimuli given when the subject is tensely waiting to react to the stimuli (reaction time determination) have a high degree of significance. It was found that the magnitude of the non-specific EEG response recorded from the vertex and the startle blink reaction is directly related to the assumed degree of the psychological significance. The short latency specific response in the somatic projection area to peripheral nerve stimulation appears to be influenced in the same manner, but the differences in magnitude are considerably less pronounced.

The EEG in the post-central regions was recorded simultaneously with the evoked responses. It was found that under the experimental condition in which the subject is tensely waiting to react to a stimulus the record contains a large amount of alpha activity. This is noteworthy, since it may be assumed that under this condition the subject is keenly alert. In contrast to this is the normal blocking of the alpha activity when the same individual carries out a simple task.

5. Glossypharyngeal neuralgia with syncope (cardiac arrest) and paroxysmal hypersecretion from the parotid gland. — L. WIDÉN, Stockholm, Sweden.

6. A case of schizophrenia with petit mal activity in EEG. — E. TROLLE, Copenhagen, Denmark.

7. Schizophrenia with petit mal activity in depth-recording. — C. W. SEM-JACOBSEN, Oslo, Norway.

8. Emotional response in human. — C. W. SEM-Jacobsen, Oslo, Norway.

''Positive'' responses such as feeling of ease and relaxation, feeling of joy with smiling and great satisfactions as well as euphoria, has been elicited from limited areas. ''Negative'' areas have been divided in areas for anxiety, restlessness, depression and even fright, to mention some. ''Negative'' regions have been but little stimulated in order to avoid unjustified discomfort for the patient. The existence also of ''positive'' and ''negative'' emotional areas within the general regions, where Parkinson-surgery is carried out, is important to point out to the doctors concerned. The areas can be mapped out by repeated electrical stimulation, thereby avoiding by accident to be left with a permanently depressed or permanently euphoric patient.

A 16 mm. sound movie was presented, illustrating ''positive'' emotional response to electrical stimulation.

9. Recent experiences from subcortical responses. — ANTOINE RÉMOND, Paris, France.

In the course of the last years we have at the Salpetrière used steriotactical methods in the frame of the surgical cure of the dyskinesies. We use an instrumentation and a technique which has been developed by ourselves and described elsewhere, and which in addition to its simplicity has the extra advantage of not necessitating anesthesia. It has been possible for us to make a number of electrophysiologic observations along the tract of the operative electrodes. The penetration tract which we have chosen has generally been occipital-pallidal. In a few cases the tract has been pre-centro-pallidal.

The electrical stimulations applied to the electrode in the course of its penetration decides subjective or objective re-actions of very great interest. We have been able to recognise a great number of conditions for sensorial responses in the visual, somesthetic, acoustic and olefactory range. We have recognized the existence of very effective sensations, pleasant or unpleasant. Finally, the usual tract of the internal capsula has permitted us to observe in detail the motricial responses which can be the origin of these structures.

10. EEG-findings in strangulation and heartstop. — Bukonjic, Jugoslavia.

11. Transistors in electroencephalography. — Frank Offner, Illinois, U.S.A.

Transistors are remarkably simple devices, which serve many of the same functions as vacuum tubes. As such, they have both advantages and disadvantages when compared to vacuum tubes. Among the advantages presented by transistors are low power consumption, small size, low noise, stability, and reliability. Among the disadvantages of transistors are temperature sensitivity, high noise, and unreliability. The apparent anomaly that the transistor can be both advantageous and disadvantageous in the same respect arises from difference in its mode of applications. The principal problem in transistor circuit design is to emphasize the desirable features of transistors and minimize their undesirable features. This requires that completely new circuit techniques be employed with transistors. It is not possible to merely ''plug-in'' transistors in a vacuum tube circuit, and at the same time achieve the rather great advantages that transistors permit. In the transistor-electroencephalograph it has been possible to keep noise level below one microvolt, have completely stable d-c response, and have the instrument operate with characteristics unchanged from the cold of high altitude aircraft use, to the heat of the jungle, where it has also been used.

12. EEG changes following withdrawal of barbiturates. — H. Wulff, Roskilde, Denmark.

13. EEG changes during and after withdrawal of Restenil. — Trojaborg and Buronjic, Copenhagen, Denmark.

SCANDINAVIAN EEG SOCIETY

Second Meeting, March 13-16, 1959

Lysebu, Oslo, Norway

Chairman: C. W. SEM-JACOBSEN
Officers: I. PETERSÉN, E. TROLLE

1. On the anti-convulsive effect of local anesthetics. — C. G. Bernhard, Stockholm, Sweden.

A survey was given of the studies at the laboratory of the effects of various local anesthetics on different central nervous functions in cats and monkeys (various spinal reflexes, efferent cortical projections, spontaneous cortical activity, post-stimulatory cortical after-discharge) which show the selective blocking effect of small intravenous doses of local anesthetics on the electrically evoked cortical convulsive activity, as well as of the studies on the correlation between the anticonvulsive action of these substances and their effect on the ephaptic type of central neurone interaction. Experiments on the relation between the anticonvulsive and the convulsive doses of different local anesthetics were also presented as well as a discussion of the theoretical basis for the clinical use of intravenous Xylocain as an anticonvulsant (cf. summary by E. Bohm below).

2. Clinical experiences of the effect of intravenous Xylocain on epileptic fits. — E. Bohm, Stockholm, Sweden.

The anticonvulsive effect of intravenous lidocaine on prolonged epileptic attacks has been studied in 52 patients. The attacks mostly occurred in the post-operative course of brain-surgery. Lidocaine has been given either in single doses during an attack or continuously in intravenous glucose or saline drips if the attacks have been repeated. The attacks which have reacted on the treatment have ceased abruptly 20-30 sec. after the injection. The amount of lidocaine, injected in single doses, has varied between 1-3 mg/kg. body-weight and in the intravenous drips 8-10 mg. lidocaine per kg. of body-weight per hour has been adminestered. The injection had no effect on the patients state of consciousness.

The lidocaine treatment has had a very good effect on grand-mal and Jackson-attacks, whereas no effect was obtained in cases of petit-mal, myoclonus epilepsia and epilepsia partialis continua. No toxic reactions have been encountered. In one case however the spasms seem to increase after an injection of 2 mg lidocaine per kg body-weight. As the lidocaine treatment of status epilepticus has no hypnotic effect on the patients this treatment has great advantages over the barbiturate method especially in the neurosurgical work. Several cases of brain-tumours were reported in which the post-operative course was complicated with a status epilepticus and a post-operative clot. The lidocaine treatment did not mask the symptoms of the clot and the patients could be reoperated without any delay.

3. Xylocain in electric convulsive treatment: studies in the mechanism of the therapeutic effect. — J.-O. Ottosson, Stockholm, Sweden.

The effect of lidocaine, given intravenously before the treatment, was studied on the seizure activity in ECT. The treatments were given in barbiturate narcosis and with complete muscular relaxation and EEG recording. The seizure duration reaches a minimum average value at 4 mg./kg. lidocaine of about 25 sec., relatively independent of individual variations of the duration of the unmodified seizure. The EEG pattern of a seizure maximally shortened by lidocaine

shows absence of frequent spikes and a rather uniform wave-and-spike pattern with decreasing frequency from 6 to 2 per sec. The muscular seizure pattern is characterized by abolition of the tonic phase.

The seizure activity modified by lidocaine compared to the maximal, unmodified activity has been shown together with Kirstein to cause a less post-treatment EEG disturbance, an unchanged memory disturbance and together with Cronholm an impaired therapeutic effect on endogenous depressions. On the other hand, increase of intensity of convulsive stimulus seizure activity unchanged increases the memory disturbance while the therapeutic effect and EEG disturbance are unchanged. The therapeutic effect on depressions is concluded to be connected to the epileptiform activity evoked at the treatment while the memory disturbance is dependent on the stimulus intensity.

4. The effects of lidocaine and lidocaine combined with Megimide on the human brain. — I. PETERSEN, Gothenburg, Sweden.

Bohm, Flodmark and Petersen illustrated electroencephalographically how the intravenous injection of lidocaine arrests status epilepticus with seizures of focal type (three cases) and pétit mal status (one case). They also studied the effect of lidocaine on the interseizure activity in about 30 patients with epilepsy. These results are published in the *Arch. Neurol. Psychiat.*, Chicago, 1959.

Blomberg, Fegersten, Flodmark and Petersen have also studied the effects on the EEG of combined Megimide and lidocaine injections. The most important observation was that the paroxysmal activity evoked by Megimide could be inhibited by a subsequent injection of lidocaine. In one case a grand mal seizure provoced by Megimide could be abruptly arrested by the immediate intravenous injection of lidocaine.

5. Intracerebral observations of the effect of lidocaine chloride. — C. W. SEM-JACOBSEN and I. PETERSEN, Oslo, Norway.

In connection with the depth-electrographic studies the effect of lidocaine chloride has been studied in patients suffering from hallucinatory psychosis and Parkinson's disease.

1. Intravenous injection of lidocaine chloride doses up to 2 mg/kg. body-weight had no effect of paroxysmal activity appearing in depth-recording. 2. Lidocaine chloride in the doses mentioned above temporarily abolished spike discharges seen in recordings from psychotic patients during psychotic episodes.

In patients suffering from Parkinson's disease the drug when given in the same amount, intracerebral at the tip of the electrode: 1, stopped temporarily the tremor, and 2, abolished the electrically evoked afterdischarges. Slowly injection of 0.10 cc. of the drug followed by another injection of 0.10 cc. 5 min. later, had no clinical effect and no effect on electrically evoked discharges. However, the effect of the drug was only followed for 20 min.

Findings by others indicate a slow diffusion of the drug in the brain tissue. This may be the reason for the absence of the effect within 20 min. More elaborate studies are in progress when clinically indicated.

6. The relationship of ventricular protein concentrations between behaviour and electrophysiological observations in man. — S. L. SHERWOOD, London, England.

The reasons leading to the present investigation were as follows:

1. The behaviour of mentally disturbed patients "improved" for periods of up to three weeks following ventriculography.

2. Abnormally high protein levels in the cerebral ventricular fluid were encountered in a number of patients with behaviour disturbances in the absence of gross neurological lesions.

3. Feldberg and Sherwood have shown that the cerebrospinal fluid of epileptic and other patients sensitizes the frog's myoneural junction to stimulation with acetylcholine, and Feldberg, Bhattacharya and Vogt in their experiments have come to the conclusion that the substance responsible for this is probably a lipoprotein. Lumbar puncture has also been used as a remedy for status epilepticus.

The protein level of the ventricular fluid of 60 patients has been reviewed and it has been found that patients with a high level of excitement and excitability usually have a ventricular protein concentration between 20 and 35 mg/ml. In some patients where a number of values were obtained, behaviour changes accompanied changes in ventricular protein levels. Patients with a high index of excitement and excitability had an increased amount of delta- and beta-activity in their EEG records in addition to the spikes or spikes and slow-waves seen in epileptics. The abundance of alpha-activity was greater in patients with lower protein levels and patients with the higher protein levels (in excess of 35 mg/ml.) had little or no alpha-activity. Three patients with slightly raised ventricular protein levels showed a large amount of spikes of approximately 10-20 msec. as recorded by depth electrodes in the rhinencephalon. An anastomosis between the ventricles and the subdural space reduced the amplitude and occurrence of the spikes and moderately attenuated or abolished the slower component.

7. Measurements of oxygen and carbon dioxide tension on the pial surface. — DAVID H. INGVAR and BO SIESJÖ, Lund, Sweden.

In cat experiments the "average" cortical oxygen and carbon dioxide tension was measured continuously by means of two new types of rapidly reacting electrodes which were applied to the pial surface. The oxygen electrode was of the polarographic type and contained multiple platinum wires melted into glass (Bürger, Lübbers and Ockenga 1958; Ingvar, Lübbers and Siesjo 1959). The carbon dioxide electrode (Hertz and Siesjö 1959) was constructed according to the principle of Stow (1957). It utilizes a plane membrane glass electrode covered by a 0.006 mm. Teflon membrane. The stability of the electrodes and of the measurements of the reproducibility was tested in experiments in which also the EEG, the blood pressure and other variables were recorded. In cortical "arousal" induced by brain stem stimulation and accompanied by desynchronization of the EEG there is usually a biphasic reaction of the cortical oxygen tension record consisting of an initial phase of decreasing tension followed by a second phase of increase. The cortical carbon dioxide tension, on the other hand, increases during arousal. The records

of the gas tensions are modified by cortical circulatory events. There observations confirm the hypothesis that the brain stem may exert an influence upon the metabolism of the cortex (Ingvar 1958). Continuous records of cortical oxygen and carbon dioxide tension during experimentally induced epileptic seizures confirmed previous observations on the dramatic changes in cortical metabolism which accompany epileptic activity.

8. The time course of sensitization following strong peripheral stimulation. — L.-E. Larsson, Stockholm, Sweden.

The excitability changes which occur after a strong peripheral nerve stimulus have been investigated in man. The startle blink reflex and the non-specific EEG response were used as test responses. It was found that the test responses were initially depressed for a period of about one second and thereafter sensitized for a period of at least 10 sec. The findings have been related to the concept of pseudoconditioning. It is considered probable that the period of sensitization is related to Pavlov's orientation reflex. It is suggested that the results may help to explain the variations in the effectiveness of conditional and the unconditional stimulus.

9. Recordings during operation in hypothermia. — Arne Lundervold, Oslo, Norway.

EEG, as well as EMG, EKG and the interacterial bloodpressure have been recorded simultaneously by means of a Grass electroencephalograph. All together, 129 patients, have been investigated, 101 patients with neurosurgical diseases and 28 ones with surgical heart diseases. The lowest temperature was 24° C.

During the cooling of the body surface, there was in the grown ups a marked increase of the frequency and a diminution of the voltage in the electroencephalograms. If muscle potentials were recorded, the EEG as well as the EKG became irregular. Heavy bleeding produced an increased frequency of the heart beat and a lowering of the bloodpressure, whereupon both these as well as the EEG, after a while, became irregular. Handling of the heart produced similar irregularities in the EEGs and EKGs.

An occlusion of the vena cava, the pulmonary artery and the aorta, was followed by a rapid increase in the slow waves whereupon all electrical activity disappeared from both hemispheres ½-1 min. later. In some instances the clamping of the vessels produced a marked muscle activity which again was followed by irregularity in the EKG. When the muscle activity ceased, the EKG became more normal again.

The return of EEG to normal after reestablishing of the circulation was more gradual and specially slow in grown ups, on an average 45 min.

Spontaneous arrest of the heart produced the same changes in the EEG as complete artificial obstruction of the input and the output of the heart. Massage of the heart was then followed by an increased electrical cerebral activity. In the beginning the EEG might be nearly normal after massage of the heart, but the activity was gradually reduced and even vigorous massage after one hour, was, after our experience, of little value, as the EEG then got quite flat. The defibrilation of the heart could re-establish the normal EKG and EEG even after a complete flattening of the EEG for more than 30 min.

10. Results of photic stimulation in a group of children with neurological, non-epileptic symptoms. — S. Brandt, Denmark.

The speaker presented results of routine photic stimulation in 150 children, from 20 months to 14 years of age, all of whom were referred to electroencephalography on account of various non-epileptic or very questionably epileptic complaints such as headache, in some cases migrainous, behaviour disturbances, abdominal colics, enuresis, endocrine symptoms, obesity, prematur pubarche or mental retardation. In 34 (23 per cent) abnormalities were precipitated, such as generalized or bioccipital sharp waves and/or paroxysmal discharges. Nine children were included with complaints generally accepted as epileptic. Children with periodic or paroxysmal complaints were not included when such complaints alternated with complaints of more typical epileptic character.

It is concluded that EEG abnormalities provoked by photic stimulation in children should be regarded as a rather non-specific indication of some electrophysiological lability but of no significant value as diagnostic criterium for the special clinical manifestations, usually covered by the term "epilepsy".

11. Bradycardia and asystole on administration of Megimide for electroencephalographic activation. — I. Petersén, U. Selldén, O. Steinwall and B. Söderholm, Gothenburg, Sweden.

Megimide acts in about the same way as other analeptics such as Cardiazol. The drug sometimes causes a number of reactions in the cardiovascular system, notably a moderate rise in the blood pressure and a change in the cardiac rhythm. The latter generally consists of tachycardia, but occasional reports of temporary attacks of bradycardia occur (Margerison, J. H. *EEG Clin. Neurophysiol.*, **1958**, *10*: 541-545).

Megimide has been used for activation in about 500 cases at the Electroencephalographic Laboratory in Gothenburg, the drug being administered intravenously in a 0.5 per cent solution at a rate of 10 mg. per min. and the maximum dose 2 mg. per kilogram of body weight.

One of our cases presented a short fainting attack at a dose of 50 mg. (0.8 mg/kg.). Electroencephalografically there appeared slow waves, suggesting cerebral hypoxia, but no epileptogenic activity. Similar EEG-findings have been described earlier by Gastaut (*EEG Clin. Neurophysiol.*, **1953**, Suppl. No. 4, 121-136) by a certain type of fainting attacks during Cardiazol activation. Our case made us suspect cardiovascular origin of the accident and since then EEG has been performed routinely by activation with Megimide. Tachycardia has been noted several times; bradycardial arrest once and distinct bradycardia twice.

In the one case bradycardial arrest followed upon 70 mg. of Megimide (1.4 mg/kg.). Within a few seconds the bradycardia resulted in asystole lasting at least 8 sec. During the following 12 sec. or so the registration was disturbed by artifacts caused by the patient's movements. The first regular beats, followed by rapid regulation of the cardiac rhythm, were seen about 20 sec. after the asystole. Clinically the patient presented simultaneously with the cardiac arrest a fainting attack with a short tonic-clonic phase.

Electroencephalographically slow waves were noted after 8 sec. of asystole suggesting cerebral hypoxia.

The two cases with a bradycardial reaction developed the complication at a dose of 50 mg. (0.5 mg/kg.) and 120 mg. (2 mg/kg.) respectively. The pulse rate being depressed during a few minutes in the one case from 66 per min. to 42 per min. and in the other from 72 per min. to 42 per min. Clinically both patients had a feeling like fainting at the end of the activation, but recovered, when the bradycardia spontaneously disappeared about 2 min. later. Electroencephalografically no changes were noted in relation to the bradycardia.

12. EEG during jet flying stress. — C. W. Sem-Jacobsen, Oslo, Norway.

THE EEG SOCIETY

Medical School, Birmingham, England

April 18, 1959

Secretary: Dr. G. PARR

68, Compton Road, Winchmore Hill, London, N. 21

1. The value of orbital and implanted electrodes in elucidating unusual sphenoidal EEG. — M. V. Driver, Maudsley Hospital, London.

Sphenoidal needles have been used for some years in investigating the electrical activity of the inferior surface of the anterior part of the temporal lobe. The clinical impression that an epileptic seizure is of temporal lobe origin is often strengthened by the demonstration of spikes or sharp waves focal at and limited to the sphenoidal electrode. Occasionally satisfactory localization of the discharge is impossible by this method and in the two cases described in this paper further investigations were made. In the first, the deduction that the unusual discharge was of frontal rather than temporal origin was confirmed by the long-term implantation of multiple-wire electrodes. In the second, implantation showed that a similar deduction apparently confirmed by the use of orbital wire electrodes, was probably incorrect.

In both cases the implantation findings were borne out at subsequent craniotomy and electrocorticography.

2. The electrical characteristics of stainless steel and silver electrodes for intracerebral electrography and polarization. — R. Cooper and W. Grey Walter, Burden Neurological Institute, Bristol.

The electrical characteristics of some materials used for indwelling electrodes of about 100 μ diameter have been examined.

Conventional stainless steel alloys are stainless and innocuous by virtue of a tough thin surface layer of chromic oxide which has a high ohmic resistance and capacitance. This in effect introduces an eluctable resistance-capacitance coupling into the input of the amplifier having values of 10 megohms and 0.1 μF. for 39 g. wire (2 mm. bared) measured in physiological saline.

In consequence, D.C. recording seems easy with stainless steel electrodes but only because steady and slowly-changing potential differences are greatly attenuated. Of the alternatives, silver-silver chloride wires are the most trustworthy, since the insoluble silver chloride film presents a lower ohmic resistance and higher capacitance (22 Kohms and 0.4 μF.) but in some conditions the metal can prove toxic. Bright silver is intermediate between steel and silver chloride, with impedances of about 3 megohms and 0.25 μF.

Since indwelling electrodes are also used to pass considerable currents through living tissue, their properties under electrolytic stress must also be considered. None of the convenient metals is ideal in this application since their peculiar surface films introduce non-linear voltage/current relationships which make study of the conditions within the tissue difficult and misleading.

A secondary effect is that the electrodes are quickly "poisoned" in protein solutions, and this action is particularly rapid and dramatic in living tissues capable of positive reaction to foreign bodies.

3. Local, specific and widespread general intracerebral responses in relation to human mentality and conditioning. — R. Cooper, H. Crow, V. J. Walter, W. Grey Walter and A. Winter, Burden Neurological Institute, Bristol.

Some correlations between cerebral and behavioural traits were shown by comparison of two cases with multiple electrodes implanted for diagnostic and therapeutic purposes. In both cases the capacity for conditioned reflex formation was impaired.

One patient, with a long history of compulsive-obsessional thinking associated with frightening auditory and visual disorders, showed almost total lack of selectivity and anticipation with excessive autonomic display. Records from intracerebral electrodes showed widespread non-specific responses to visual and auditory stimuli, in the frontal lobes, subject to marked habituation.

The other patient gave abundant conditioned responses, but these were quite erratic and never corrected. Autonomic responses were minimal and the P.G.R.s in particular suggested an inability to discriminate between neutral, conditioned and unconditioned stimuli.

In this patient the first EEG showed spectacular frontal spike response to photic stimuli, but this never recurred, and intracerebral recording showed no generalized frontal region response to auditory or visual stimuli, though there were clear responses to visual stimuli in the optic radiations and occipital cortex. This patient had lifelong episodic migrainous headaches, culminating in a state of chronic depressive martyrdom.

A plausible explanation of the findings is that the mental disturbances were associated with intrinsic anomalies in the functional relations between the dif-

fuse projection systems, the limbic cortex and the hypothalamic-autonomic mechanisms. It is suggested that these anomalies were such as to produce impoverishment of adaptive repertoire with consequent failure to control external events.

4. An attempt to select sites for focal frontal leucotomy and to produce focal lesions by electrolysis, using multiple indwelling frontal electrodes. — H. J. Crow, D. G. Phillips and G. L. Alexander, Burden Neurological Institute and the Frenchay Hospital, Bristol.

Sem Jacobsen has demonstrated the temporary abolition of symptoms in the mentally ill by stimulation through frontal intracerebral electrodes.

If we consider the current as producing reversible changes in the frontal white fibres and temporarily interrupting the passage of physiological impulses, this suggests a method of finding by trial and (reversible) error small bundles of frontal fibres whose interruption could relieve symptoms in some patients.

Such tracts, when found, could be destroyed by electro-polarization with the hope of long-term relief.

Treatment was tried on (*a*) a female of 36 with 12 years history of fear, depression, obsessions and delusion with insight after standard treatment had failed. Case (*b*) was a female of 60 with life-long migraine and suicidal depression. In each case the surgical procedure was the same: through bifrontal holes 4 sheaves of electrodes (7 per sheaf) were placed fanwise in the coronal plane of each frontal lobe immediately anterior to the tip of the ventricles. In case (*a*) very small currents passed through each electrode produced no effect except for marked and repeatable changes in symptoms with five electrodes. Destructive polarization through these electrodes produced complete relief, but the severe tension recurred and 10 weeks later she was again severely ill but was not affected by obsession and delusions.

Case (*b*) suffered two small focal lesions on insertion of the electrodes, but was markedly improved. Destructive polarization was carried out at two points symmetrically related to the surgical lesions.

5. The value of stereotaxic recordings at operation and of long-term implanted electrodes in planning leucotomies. — S. L. Sherwood, Severalls Hospital, Colchester, Essex.

Leucotomy is generally held to change the patient's behaviour so that the most disabling characteristics of the illness are attenuated by producing 'frontal lobe deficit'. Many thousand leucotomies have shown that the effect is quantitative, but this does not rule out the anatomically localized function: this possibility is supported by the efficacy of limited sections and by the consideration that the more tissue is disconnected the more likely it is that foci of unwanted function are included.

To test this proposition, 23 leucotomy candidates were examined by taking EEGs, Megimide and Penothal administration, and the response to click and flash stimuli. Of these, 7 proceeded to operations on the temporal lobes or treatment other than leucotomy, 12 had stereotaxic cortical or subcortical recordings at the time of operation, and 4 had implanted multiple depth electrodes for several weeks before and after leucotomy.

The records of 8 patients under anaesthesia had apparently localized paroxysmal disturbances—judged in analogy to scalp-EEG abnormalities in the first place. This judgement is open to doubt, even though Pentothal scalp-EEG records were available for comparison.

Consistency in the findings when patients were compared clinically and electrographically shows that localized disturbances are not common to the patients examined. Sections intended to isolate these loci were made, keeping the electrodes in place until so-called 'de-afferentation' rhythmic β activity appeared. Of the patients, 4 remained in hospital, 2 considerably improved, 2 were unchanged, 3 were able to leave, and 1 died. Of the remaining 8 patients whose records show no localizing features, 6 have left hospital (1 unexpected suicide) and 2 are in hospital but much improved. Of 4 patients with long-term implanted electrodes, 1 died and 2 have been able to leave hospital; 1 is in hospital much improved.

There is hope that more extensive and detailed studies will yield more valuable information than the straightforward record. If these figures were confirmed by large matched series it would demonstrate the value of extensive subcortical recordings, as the results are better than the statistics without them.

6. Long-term EEG investigations of idiopathic epilepsy before and after stereotaxic subcortical lesions. — R. Lohmann, Cologne and Oxford.

Five cases were subjected to stereotaxic subcortical lesions by F. Roeder and H. Orthner (Göttingen University) for treatment of idiopathic epilepsy. In 3 cases the lesions were caused by electrical coagulation in the dorso-medial nucleus of the thalamus, in 1 case in the right fornix and in the last case in the *massa intermedia thalami*. One to three weeks after operation all cases showed an increase in abnormal brain activity, including epileptic discharges; these persisted, although clinically the major convulsions decreased in 2 cases. Unilateral lesions in the thalamus produced distinct differences in the records from both hemispheres which were not observed before operation. Petit mal attacks which were frequent before operation were markedly reduced and finally disappeared after coagulation of the *massa intermedia* in one patient.

7. Further studies of response to stimulation during sleep. — I. Oswald, Anne Taylor and M. Treisman, University of Oxford.

In order to study galvanic skin responses (Tarchanoff effect) during sleep we have used repetitive stimulation by brief tones. The GSR soon shows habituation to zero during wakefulness and does not return during drowsiness. As sleep deepens the GSRs of some return after a period. Their latency is longer during sleep and tends to become irregular; in some it is finally random during sleep characterised by high voltage waves (1 c/sec.) in the EEG. During these, apparently spontaneous GSRs often occur in the absence of deliberate external stimulation. A return to light sleep diminishes the randomness or may abolish the GSR. It is thought that the observation may be related to the varying strength of tonic descending inhibitory control exerted on the upper reticular formation.

While in some cases a novel arousal stimulus interspersed between the repetitive auditory stimuli can cause the appearance (for the first time during

sleep) of GSRs to the repetitive tones, yet in other cases a non-specific disturbance — e.g. turning over in sleep — can be associated with an abrupt change from a condition in which GSRs occur with the usual latency to most of the stimuli to a condition in which the GSRs become and remain random.

8. The effect of drugs on conditioned arousal responses. — B. J. Key and P. B. Bradley, Medical School, Birmingham.

This study is an attempt to compare the effects of incremental doses of some drugs on conditioned and unconditioned auditory induced arousal responses in chronic cat preparations carrying implanted cortical recording electrodes. The conditioned response was obtained by pairing an electric shock with the particular tone chosen. The effect of a drug on unconditioned arousal produced by noise qualitatively different from that of the conditioned stimulus was also observed.

Doses of 5 - 10 mg/kg. chlorpromazine intraperitoneally produced a rise in the thresholds for conditioned as well as unconditioned arousal responses. Both responses were blocked completely following 15 - 20 mg/kg.

Lysergic acid diethylamide (LSD 25) in doses of 5 - 20 μg/kg. intraperitoneally had no effect on conditioned arousal responses but produced a decrease in the threshold for arousal evoked by a neutral stimulus. In addition, a tone to which the animal had been previously habituated produced a marked response after small doses (5 - 10 μg/kg.) of this drug.

Doses of 0.5 - 1.5 mg/kg. atropine produced a marked rise in thresholds for both types of response without affecting the thresholds for behavioural arousal. After a dose of 1.5 - 2.5 mg/kg. EEG arousal responses were blocked completely, as the electrical activity of the cortex became dominated by slow waves and spindle bursts.

Increasing the dose to 4 mg/kg. still produced no effect on the conditioned behavioural arousal threshold, but the threshold for arousal produced by the neutral tone increased as the animal gradually became habituated to the stimulus.

9. The value of Metrazol and Megimide in the location of epileptogenic lesions. — W. A. Kennedy, Maudsley Hospital, London.

Many workers have emphasized the value of convulsant drugs, particularly Metrazol, for the localization of epileptogenic areas. Others have relied on sleep records, particularly barbiturate-induced sleep. At the Institute of Psychiatry we have used Megimide and Metrazol in the investigation of epileptic patients. In all, 28 patients have been activated by Metrazol and 27 by Megimide — 12 received both.

Metrazol lateralized the lesion in 16 out of 21 patients in whom the lesion had been localized by other methods of EEG recording. Megimide lateralized the lesion in 13 out of 19 patients.

It is concluded that both drugs are of value in localization of epileptogenic lesions but are inferior to Pentothal-induced sleep, particularly in temporal lobe epilepsy.

10. A comparison of the EEG in normal and hypothyroid rats at different ages. — P. B. Bradley, J. T. Eayrs and K. Schmalbach, The Medical School, Birmingham.

The EEG of rats made hypothyroid from birth (cretins) with radioiodine or methyl thiouracil has been compared with that of normal littermates. At 15 days records from both types showed little activity but those of the cretins tended to be flatter; at 18 days more activity was seen, but this was still less in the cretins; the 24-day normal rat showed rhythmic and slow potentials usually associated with drowsiness, which could be blocked by sensory stimuli. These did not appear in the cretin, although it was less active than normal.

These differences were often more accentuated at 36 days, and were still present at 60 days. In the older animals it was found that while the normal rat responded well to rhythmic sensory (visual) stimulation such responses were either absent or of low amplitude in the cretin.

It is thought that the differences in electrical activity must reflect some defect in the cerebral structure and function and are not merely due to differences in bodily activity or electrode placement; it is also unlikely that they are merely quantitative.

The administration of tri-iodothyronine produced some improvement in the cretin, suggesting that the changes are to some extent reversible. Comparable observations have been made on the learning capacity of similarly treated rats in which a severe but partly reversible impairment occurs as a result of thyroidectomy at birth (Eyrs and Lishman, 1955) but not when the operation is delayed until the 24th day (Eayrs, unpublished).

The absence of slow waves from the EEG of the cretin is consistent with the view that slow potential changes in the EEG are associated with dendritic potentials, while the apparent absence or diminution of responses to sensory stimulation could be attributed to reduced inter-neuronal connectivity.

11. The prognosis of infantile spasms with and without treatment by ACTH. — P. M. Jeavons and B. D. Bower, All Saints Hospital and The Childrens Hospital, Birmingham.

Thirty-one infants who have developed infantile spasms and who were not treated with ACTH have been followed with regular clinical and EEG examinations for 1½-4 years. Twenty-five whose first EEG was taken before the age of 1 year all had abnormal record; in half this was sufficiently chaotic to be labelled hypsarhythmia, while the other half showed more organized epileptic records. In the majority there was an improvement as the patients grew older. At 2½ only 2 had hypsarhythmic records, 12 had an epileptic one and 9 had a normal one. The severity of the initial abnormality seemed to have no individual prognostic significance.

EEG improvement was paralled by improvement in epilepsy; at 2½ spasms had ceased in 10 patients, but mental retardation showed little improvement and only 2 achieved normal mentality.

A group whose condition was probably due to early brain damage showed less improvement in the EEG than those where the insult occurred later. There was little difference between the groups in mentality and eventual freedom from spasms.

A small group of patients has recently been treated with ACTH. EEGs taken twice weekly improved after a week, and this was paralleled by diminution or cessation of spasms.

12. EEG, cardiovascular and respiratory changes in monkeys subjected to extreme hypothermia. — R. Bryce-Smith, H. G. Epstein and P. Glees, University of Oxford.

In 20 experiments, monkeys were subjected to extreme hypothermia (19° - 20°C) and a number of physiological reactions such as EEG, heart rate and respiratory changes were recorded simultaneously.

If ether was used as the initial anaesthetic it was stopped when the rectal temperature had fallen to about 28°, and in this way EEG records could be obtained which were more closely related to the effects of hypothermia than Nembutal records.

This type of record shows slow wave activity of low voltage as low down as 19°C. Most disturbing, however, are the electrical discharges from muscles (shivering), which can be abolished with the i.v. injection of 3 mg. suxamethonium. The injection of Bemegride causes a distinct activation of the EEG, which can lead to spike discharges.

On the average the heart rate dropped from 200 per min. at 35°C to about 60 per min. at 21°C. The rate of respiration fell progressively during cooling, but the fall was not as consistent as the drop in heart rate.

1 We gratefully acknowledge a grant from the Medical Research Council, London.

13. Functional disturbance associated with the development of haematogenous brain abscesses. — E. J. Newton, Smethwick Hospital, Birmingham.

Though the majority of abscesses arising from blood-borne infection occur in or near the cerebral cortex, EEG localization is not always precise. Neither does the EEG always distinguish between an abscess and other kinds of space-occupying lesions (e.g. hematoma) or from non-space-occupying infective disorder such as meningitis.

Patients are often ill, restless and in need of urgent surgical treatment. For this reason the EEG is sometimes not taken prior to treatment of the abscess. When the examination is made the EEG record is invariably found to be abnormal, with delta activity, usually focal but sometimes diffuse and bilateral.

A high incidence of fits, both focal and generalized, has been noted in 94 cases during the genesis of the abscess. In some cases no fits occurred during the acute stage but began a year or moreafter treatment. The frequency of epilepsy is in keeping with the supposition that abnormal EEG activity is probably always present in these cases in the acute stage.

Multiplicity of abscesses may cause difficulty in EEG localization, but in the majority of cases the abscess is single. It is suggested that coincidental healing abortive foci of pyogenic infection may be electrically active and so confuse the record.

In the group of cases studied there was a tendency for the solitary abscesses to have sites of predilection: these were pre-Rolandic and parietal.

CENTRAL ELECTROENCEPHALOGRAPHIC ASSOCIATION

Indianapolis, Indiana

May 1, 2, 1959

Secretary : FRANCIS J. MILLEN, M.D.

208 E. Wisconsin Avenue, Milwaukee, Wisconsin

1. Chronic encephalopathy association with the Vogt-Koyanagi syndrome. — Philip T. White and Harold Booker, Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana.

The Vogt-Koyanagi syndrome and its variants are characterized by uveitis, alopecia, poliosis, vitiligo and dysacousia. It has been called uveo-encephalitis because of a relationship between encephalitic or meningitic signs and involvement of the uveal tract. Previous work suggested that this was an encephalitic process with secondary involvement of the visual apparatus. A case is presented to support this concept. The patient demonstrated signs of Vogt-Koyanagi syndrome with the onset of seizures four years prior to visual changes. Studies undertaken failed to reveal any structural intra-cranial lesion. Electroencephalograms done during her hospitalization showed continuous seizure-like activity consisting of generalized synchronous high amplitude spikes and slow waves with a frequency of 4 or 5 c/sec. These were interspersed with brief periods of normal activity. This persisted over a period of months. Later changes consisted of low voltage slow waves, more clearly noted throughout the right hemisphere, with paroxysms of low voltage sharp waves and rhythmic slow waves throughout the right hemisphere. The electroencephalogram, many months after the onset of her difficulty, showed high amplitude rhythmic synchronous slow waves, sharp waves and spikes and independent paroxysms of slowing and spike activity on the right. This case illustrated the primary involvement of the central nervous system with subsequent involvement of the visual apparatus after a prolonged time. The electroencephalographic changes reflected involvement of diencephalic structures as well as more generalized involvement compatible with a chronic encephalitic process. The term uveo-encephalitis was considered applicable.

2. EEG changes associated with bronchogenic CA with autopsy studies. — Philip T. White, Richard Taylor and John Nelson, Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana.

It was presumed that the electroencephalogram might be helpful in detecting metastatic disease. Previous studies had supported this concept but failed to make correlation with autopsy studies or failed to take into account other diseases capable of producing changes in the electroencephalogram. In this study, electroencephalograms were conducted on fifteen pa-

tients with bronchogenic carcinoma studied at autopsy. One patient with a normal electroencephalogram had a normal brain. Non-focal changes of varying degree occurred in eight cases. In two, metastatic lesions of the brain were detected. In those without metastatic lesions, other neurologic or systemic diseases could be assumed to produce the changes seen in the electroencephalograms. In six patients, focal electroencephalographic changes were present. Four of these were related to metastatic disease, one was secondary to intracerebral hemorrhage and one was related to diffuse atheromatous changes. Of the fifteen patients, six had metastatic brain lesions and all were multiple. In two cases where the metastases were small and multiple without edema, electroencephalograms showed only non-specific changes. Of the patients with metastatic lesions associated with edema, all of the electroencephalograms showed localization corresponding to the area of most marked metastatic involvement and also corresponding to clinical signs. Metastases to deeper structures were not always reflected in the electroencephalogram. It was concluded that electroencephalographic changes must be evaluated in conjunction with a neurological history and examination so that other causes for electroencephalographic changes are not overlooked. Electroencephalograms may not eliminate the possibility of metastatic disease nor necessarily detect the presence of multiple lesions, but focal electroencephalographic changes when evaluated critically and associated with specific neurologic signs may well be a valid indicator that cerebral metastases exist.

3. Correlation of EEG and temporal lobe seizure patterns. — CHARLES A. BONSETT, Indianapolis, Ind.

Seventeen cases were presented. Sixteen of these had a temporal focal spike. One had repeatedly normal records including sleep activation. Four additional cases were presented with intracranial pathology demonstrated by angiography and/or pneumoencephalography. Spike discharges in these cases were associated with other EEG abnormalities.

Films and complete records were available for examination.

4. Localization factors. — IAN HAY BROWN, M.D., Miami Valley Hospital, Dayton, Ohio.

A review is presented of the technical factors involved in the localization of patterns, normal and abnormal, appearing in the electroencephalogram. The recording techniques simply analyzed consist of unipolar and bipolar recordings, each with it's own particular rule-of-thumb principles. The term unipolar is preferred to that of monopolar because of the latter's conventional usage signifying scalp-ear recordings, which latter may be actually a part of the bipolar type recording. Illustrations are presented demonstrating phase reversal and ''voltage depression''.

5. Cerebral metabolic and circulatory studies during Metrazol convulsions. — B. ABREU, C. BONSETT, P. WHITE, P. GRANT and J. MOSIER, Indianapolis, Indiana.

6. On conditioned alpha enhancement. — JOHN A. STERN and HENRY LACKNER, Department of Psychiatry and Neurology, Washington University School of Medicine, Seattle, Wash.

Conditioned alpha enhancement through pairing an auditory with a visual (light off) stimulus has been reported, in the Russian literature, to produce conditioned alpha enhancement. Experiments conducted by the above investigators were unable to obtain conditioned alpha enhancement using two different types of conditioning procedures. We did however observe that in response to a series of auditory stimuli(presented during a pre-conditioning ''adaptation'' period) there is a relative enhancement of alpha activity during trials 10-20 of sound presentation. The results are compared to those obtained by Darrow *et al.* and by Williams.

7. Effects of rhythmic multiple flashes on human EEG. — W. T. LIBERSON, Veterans Administration Hospital, Hines, Illinois.

Slow waves of 2-5 c/sec. frequency may be driven in the parieto-occipital regions without any activating drugs by two or three consecutive flashes (with an interval of 70 msec.) repeated at the same frequency. They are more often observed in children of 4-10 years of age than in adults. No definite clinical correlations have been found.

Just as in the case of fast waves driven by single flashes, one or several extra slow waves of the same frequency may be recorded after the discontinuation of the flicker. An hypothesis was discussed according to which driven waves constitute a series of evoked responses always having the same time characteristics but each interrupted by successive flashes, thus giving an impression of synchronized waves the duration of which is a function of the driving rhythm. This hypothesis proved to be untenable as the phase reversals of the driven waves are so timed during the interval between flashes as to suggest a complex plastic phenomenon, rather than a mere succession of evoked responses with time characteristics independent of the timing of each succeeding flash. In cases where driven responses were obtained to paired flashes and not to single ones, the latter became effective after a period of stimulation with paired flashes.

8. Late evoked potentials and driven responses in the hippocampus of the unanesthetized rat. — W. H. LIBERSON and PAUL ELLEN, Veterans Administration Hospital, Hines, Illinois.

1. An electrical stimulus applied to one hippocampus of the rat (chronically implanted electrodes; 1 msec. pulses; 5-10 V.) may elicit in the opposite hippocampus late evoked potentials in addition to those occurring within the first 40-50 msec. and which were studied in the past by the authors. The crests of the additional most consistent negative waves usually occur 120 and 350 msec. following the stimulus, suggesting correlation with previously studied excitability cycle (Liberson and Cadilhac).

2. Electrical stimuli repeated at a frequency of 2-5 c/sec. elicit, after several trials, driven responses analogous to those elicited in the human EEG by flicker (at times 80 trials of 20 stimuli each are necessary). One or several of the driven waves may persist after the end of the stimulation. The analysis of the genesis of these driven responses show that their occurrence coincides with a definite change from the sequence of evoked potentials elicited by single stimuli. Thus, late evoked potentials occur earlier for the 3 c/sec. stimuli than for 2 c/sec. rhythm and still earlier for the 5 c/sec. rhythm. This observation sug-

gests the possibility of an experimental analysis of the phenomenon of "driving".

3. Occasionally, evoked spikes could be conditioned, occurring between the stimuli or after the end of the stimulation, at times repeatedly. The time of their appearance is a function of the conditioning rhythm.

9. Presentations of specialized research projects. — Morris Aprison, Charles Ferster and Richard McCaman, Psychiatric Research Institute, Indianapolis, Indiana.

10. Some changes in patterns of convulsive behavior after various ablations of the brain in the salamander. — J. J. Peters and A. R. Vonderahe, Cincinnati, Ohio.

In the salamander, an ablation of the telencephalon leaves the seizure pattern induced by Metrazol almost unchanged: the animal exhibits hypersensitivity, gasping, and writhing, and undergoes a convulsion with tonic and clonic phases. After a removal of the prosencephalon, the convulsion induced by Metrazol shows a more severe tonic phase, but hypersensitivity and the clonic phase are no longer evident. After a removal of both prosencephalon and mesencephalon, the salamander can still walk, swim, and right itself, but Metrazol fails to evoke seizures with either tonic or clonic components. After an ablation of the entire brain, the salamander loses the ability to walk, swim, or right itself, and an injection of Metrazol is followed by vigorous writhing and an erratic placement of limbs.

11. Correlation of EEG and neuropsychological studies in organic brain disease. — Hallgrim Kløve, Philip White and Richard Taylor, Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana.

This study was undertaken in order to determine a possible differential effect of brain damage on Wechsler-Bellevue Scale (Form I) when groups were composed according to electroencephalographic criteria.

Procedure:

Four groups of patients with verified brain damage were composed:

Group I: (37 patients with predominance of EEG-disturbance over the right hemisphere).

Group II: (42 patients with predominance of EEG-disturbance over the right hemisphere).

Group III: (45 patients with abnormal EEG, but no definite lateralizing predominance (generalized EEG)).

Group IV: (61 patients (also brain damaged), but with normal EEG).

Wechsler-Bellevue was administered to each patient. Intergroup results were compared. No significant differences between groups with respect to age, education, and time between testing and EEG were found.

Conclusions and implications:

EEG-lateralization to the right tended to suppress performance subtests of W-B while lateralization to the left tended to suppress verbal subtests. Groups with generalized and normal EEG showed no difference between verbal and performance subtests, but the groups were different in absolute level.

A comparison of the Halstead Impairment Index for the four groups was also performed. The Impairment Index was in the brain-damaged range for all four groups and there was no significant differences between the groups. This may be interpreted to indicate that the Halstead Impairment Index may be more sensitive to the organic condition of the brain than the EEG and the Wechsler-Bellevue Scale.

12. Human stereotaxic methodology: procedure in electrical recording from the basal ganglia and brain stem in human subjects. — George C. Manning, Jr., Warren C. Hastings and John W. Bossard, Fort Wayne, Indiana.

Data was presented to demonstrate the degree of Xray magnification of various objects at varying distances from the Xray film and from the central ray, to demonstrate that objects placed at different distances from the film and the central ray are NOT magnified in a simple arithmetical proportion.

Data was also presented to demonstrate the effect upon the Xray magnification of a point having a constant position in space, when there is a shifting relation between the Xray tube and the film used to demonstrate the point. The conclusion being that in order to make valid calculations of manification that an absolutely constant tube-film relation must be maintained.

The prerequisites for exact calculation of Xray magnification are presented in detail.

The method of plotting the actual Xray projection, of points of interest measured on the films, onto graph paper was demonstrated. The method of determining the decimal factor by which to multiply these measured distances in order to determine their actual spatial coordinates was also demonstrated.

The use of an external phantom model to determine directly the angular and linear relationship of two points in space was demonstrated. The use of the human sterotaxic device designed by us, in association with Mr. Henry Schryver, was demonstrated. This device differs from previous human devices in that its principal traverse is in an anteroposterior direction obviating the necessity for arcuate members.

13. The convulsive patterns provoked by Indoklon, Metrazol and electro-shock. Some depth electrographic observations in human patients. — Gian Emilio Chatrian and Magnus C. Petersen, Rochester State Hospital, Rochester, Minnesota.

Intracerebral recordings were taken by means of stainless steel multielectrode leads in 5 schizophrenic patients during 21 convulsive seizures provoked by inhalation of hexafluorodiethyl ether (Indoklon), intravenous injection of pentylenetetrazole (Metrazol) and electro-shock. The leads were introduced into the brain substance through two frontal burr-holes which were used later for prefrontal lobotomy. At the present, platinum-irridium leads are also used in our laboratory whose chief advantages for intracerebral recordings appear to be: an opacity to X-rays considerably greater than that of stainless steel, a lower interelectrode impedance and a tensile strength which is fairly close to that of stainless steel.

The patterns which characterize the prodromic, tonic and clonic phases of the seizure showed some individual and regional variation but were fairly consistent for each cerebral area and for the same patient from one seizure to another. This is regardless of the nature and mode of administration of the convulsant. The post-convulsive patterns also were fairly constant however the seizure was induced. These findings suggest that the convulsant agents investigated act upon the human brain through a common operating mechanism.

14. Fourteen and six per second positive spike activity in the EEG of identical twins and family. — FRANCIS J. MILLEN and KENNETH WINTERS, Milwaukee Children's Hospital, Milwaukee, Wisconsin.

The case history and family history is presented of two identical twins age 5 years both of whom suffered with recurring, episodic, intermittent attacks of abdominal pain, associated with anorexia, nausea, vomiting, and having identical electroencephalographic abnormalities of 14 and 6 per second positive spike dysrhythmic discharges in temporal and occipital lobes. The mother, age 38 years suffered with migraine headaches since childhood and had a normal electroencephalogram. The father, age 38 years had similar abdominal pain attacks in childhood and had a normal electroencephalogram. A brother age 18 years suffered with episodic abdominal pain attacks during adolescence for several years and had a normal electroencephalogram.

Repeat electroencephalograms were done on both twins and revealed consistently the positive, spiking dysrhythmic activity.

The literature concerning so called ''Abdominal Epilepsy'' was reviewed briefly pointing up the clinical characteristics of the disorder. Electroencephalographic data from the EEG laboratory at Milwaukee Childrens Hospital on patients with 14 and 6 per sec. positive dysrhythmia and the second group of patients with a clinical complaint of abdominal pain syndromes was presented. Of 275 clinical cases showing 14 and 6 per second positive dysrhythmia, 34 of the patients had as a chief complaint abdominal pain syndrome (12.7 per cent). Of 86 clinical cases presenting with the chief complaint of abdominal pain syndromes, 31 had 14 and 6 per sec. dysrhythmia (36.0 per cent). Of 275 clinical cases with 14 and 6 per sec. dysrhythmia, 5 families were found in whom 14 and 6 per sec. positive spike dysthythmia was present in two or more siblings or members of the family.

15. A study of the use of recorded music in the EEG laboratory. — HENRY VIET, L. C. MUSKATEVC and L. MOLITOR, Milwaukee, Wisconsin.

16. EEG pharmacology. — DOUGLAS GOLDMAN, 179 East McMillan St., Cincinnati 19, Ohio.

The effect of a number of drugs on the electroencephalogram was illustrated, both without and with Pentothal activation. The importance of recognizing that some functional changes take place without being evident in standard EEG recordings by the usual techniques was clearly demonstrated. The value of Pentothal for bringing to light such changes was shown.

17. An EEG tachometer or wave by wave frequency indicator. — RICHARD N. VIETH, CHESTER W. DARROW, JUDITH M. MALLER and JERE P. WILSON, Institute for Juvenile Research and Illinois Public Welfare, Mental Health Fund, Chicago.

In an effort to obtain a continuous indication of moment to moment changes in EEG frequency this device employs a measure of wave length. The amplitudes and filtered output of an EEG channel controls discharge of a thyratron in the first stage of the instrument to provide, independently of amplitude, a triggering of a second stage thyratron with each wave. The voltage built up in the second stage during each wave before triggering by the next is registered as vertical displacement from the base line.

The method presents difficulty owing to the impossibility of simultaneously registering two or more different concomitant frequencies. However, a continuous indication of changing *dominant* frequencies at different frequency levels becomes possible by the use of different input filters.

Illustrations from results obtained with inputs from separate and combined frequency oscillators and from human EEG's are presented.

18. The relation of EEG phase differences between areas to local frequencies. — JUDITH M. MALLER, CHESTER W. DARROW, JERE P. WILSON and RICHARD N. VIETH, Institute for Juvenile Research and Illinois Public Welfare Mental Health Fund, Chicago.

Theoretically there are inseparable relations between frequency and phase. Two wave patterns of identical frequency can be continuously in-phase or 180° out-of-phase with one another, or one can continuously lead or lag the other. On the other hand, wave patterns of different frequencies will, necessarily, beat with each other after the manner of a heterodyning radio. As shown by instrumental phase comparison, beats will occur as the faster of two channels, controlled by different frequency generators, from a lagging position, catches up to, and then leads the slower channel. By combining instrumental phase comparison with the tachometric frequency indicator described in the preceding paper phase changes associated with variations in frequency are readily demonstrated. The application of these methods to the recording of phase relations between brain areas and the accompanying local frequency changes are illustrated for the conditions of sleep and stimulation.

19. Laterality of change in the EEG during right and left activity. — JERE P. WILSON, CHESTER W. DARROW, RICHARD N. VIETH and JUDITH M. MALLER, Institute for Juvenile Research and Illinois Public Welfare Mental Health Fund, Chicago.

In continuation of a study, preliminary results of which were reported to Central EEG Association two years ago, the motions of writing a word on an imaginary blackboard were repeated eight times at 15 to 20 second intervals with one hand, then repeated using the opposite hand and a different word.

In 20 subjects a larger ''per cent time alpha'' is found for the three second interval prior to writing than during the three second interval following the initiation of writing. In the period during writing there is a larger ''per cent time alpha'' recorded from

the right than from the left occipital hemisphere, while prior to writing, alpha is nearly equal in the two hemispheres. These results are obtained regardless of hand used, order of use of hands, or whether the subject is writing the first or last three repetitions of a word.

In contrast to writing, a simple loud auditory stimulus, a gong, while effecting a reduction of "per cent time alpha", did not produce appreciable difference between hemispheres.

The tendency towards left lateralization of occipital blocking during the handwriting performance found in this study and the clinical reports of impairment of verbal ability following left hemisphere brain damage are interpreted as parallel reflections of the greater contribution of the left hemisphere in the organization or control of verbal-motor behavior.

20. Post ictal studies in children. — PHILIP WHITE and GEORGES MULLER, Indianapolis, Indiana.

21. Electro-oculographic measurement of eye motion during the perception of apparent vision. — CHRISTINE KRIS, Boston, Mass.

22. Cortical and subcortical recording in a patient with massive spasm. — R. BICKFORD, H. SVIEN, H. KEITH and D. KLASS, Rochester, Minnesota.

23. Electroencephalographic study of mental retardation (exclusive of cerebral palsy and clinical epilepsy). — ERNA L. GIBBS and CATHERINE RICH, Chicago, Illinois.

Electroencephalograms, awake and asleep, were recorded on 1,200 feeble minded subjects who did not have cerebral palsy or clinically evident epilepsy. The cases were graded according to the severity of the mental defect and according to age. They were further subdivided into the following two etiologic groups: (1) unknown cause, and (2) encephalitis and organic brain damage. Cases with specific etiologies such as hydrocephalus, microcephalus, phenylpyruvic amentia were not included because previous studies have shown that these diagnostic groups have more or less characteristic electroencephalographic abnormalities.

The present study shows that the amount of electroencephalographic abnormality among these rather non-specific types of retarded patients is high: 50 per cent had abnormal electroencephalograms. It is highest among those with I.Q.s below 40: only 39 per cent had normal electroencephalograms, 49 per cent had seizure discharges, and 12 per cent had additional abnormalities such as asymmetries and slow activity. This most severely retarded group not only showed the highest incidence of specific abnormalities, but they also had the highest incidence of abnormal sleep spindles.

The group, where there was a known cause for the mental retardation had slightly more abnormalities of all types; 53 per cent had seizure discharges, 7 per cent other abnormalities, and 40 per cent were normal. Among the mentally retarded due to unknown causes, 55 per cent were normal.

In all categories age was an important determinant; the electroencephalograms were more normal below age 1 and above age 30 regardless of symptomatology or etiology.

24. Electroencephalographic abnormalities caused by common infectious diseases of childhood, without clinical evidence of encephalitis. — FREDERIC A. GIBBS, Chicago, Illinois.

Electroencephalograms were recorded on 1,228 children during and after measles, mumps, chickenpox, scarlet fever, and rubella without clinical evidence of encephalitis. Slow activity, unrelated to fever, occurred in 50 per cent of children with measles, 30 per cent with mumps, 22 per cent with chickenpox, 21 per cent with scarlet fever, and 12 per cent with rubella. In most cases the slow activity disappeared in 10 days, but in 2 cases it was replaced by spikes which gradually increased in number and voltage. Eventually convulsive seizures occurred in these two cases.

Disappearance of electroencephalographic abnormality does not prove that the infectious process did not injure the brain. Symptoms suggesting brain damage have not occurred among children without electroencephalographic evidence of brain involvement during the acute phase of their illness, but intellectual defects and behavior disturbances have occurred in some cases where such involvement occurred but in which the follow-up recording was normal.

25. Hypsarhythmia and ACTH therapy. — C. G. GLENN and R. KNUTH, Decatur, Illinois.

Three children under the age of two and one-half with acquired infantile spasms of less than three months duration and showing hypsarhythmia in their electroencephalograms were treated with short courses of ACTH. They all stopped having seizures and the electroencephalograms returned to normal.

ITALIAN SOCIETY FOR EEG AND NEUROPHYSIOLOGY

Messina, May 9-10, 1959

Secretary: H. TERZIAN

Clinica Neurologica dell'Università di Padova, Italy

1. Unusual finding of periodic spike and polispike activity during coma in two cases of subacute encephalopathy anatomically verified. — G. ALEMÀ, R. VIZIOLI and G. C. REDA, Rome.

The cases of two female patients of 49 and 56 are described in which a rapidly lowering of intellectual capacities followed a short period of psychical troubles consisting respectively in an agitated state and in a depressive state. After a short period of confusional state coma followed. During coma in one of the two cases a diffuse myoclonic state was remarked: flexer myoclonus of arms and head, enhanced by stimuli, was the main character. The patient was in an hypertonic state; in the second patient flexor myoclonic jerks were not spontaneous but they could be elicited by strong stimuli and had a

short duration. The EEG record registered till death in one of the two patients consisted in periodic bursts (1/sec.) of spikes and/or polispikes non synchronous with myoclonic jerks and independent by pulse and breathing. Necropsy showed in both cases a thinned grey substance with diffuse neuronal loss and oedematous state. No inflammatory components were present.

Although the cases are similar to those of Jones and Nevin, there are some differences which are briefly commented and the possibility of a new electro-clinico-anatomical entity is considered.

2. Electromyographic study on the effects of depressant drugs of the central nervous system on the palmar chin reflex. — T. Bonaretti and P. Rovetta, Milano.

The effects of parenterally administered thiobarbiturate, promazine, methocarbamole, diazine-triazine and a morphine-like substance on the palmar chin reflex of Marinesco and Radovici were studied. The responses were evoked by mechanical stimulation of the palmar skin (thenar) and by electric stimuli applied to the median nerve. A density index of the response was used for the calculation of the reflex intensity.

The thiobarbiturate depress the reflex response until the abolition with doses of 200-300 mg. Strong depression is obtained also with the morphine-like drug which in cases of weak reflex can abolish the response. The promazine compounds, in doses of 50 mg. i.v., reduce the reflex response of an interferent type down to a response of single unit motor potentials. The so-called myorelaxants, such as methocarbamole and diazine-triazine at i.v. doses of 2 g. and 120 mg. respectively, decrease the reflex intensity of about 50 per cent by reducing the amplitude and the density but they never give rise to a single unit motor potentials response.

3. The statistical behaviour of discharge-intervals of the motor unit in atrophia muscularis myelopathica. — V. Bergamini, S. Broglia, L. Ravizza and A. Riccio, Torino.

Large statistical analysis of the discharge-intervals of the motor unit (Tokizane's method) may induce interesting neurophysiologic and physiopathologic deductions.

In the past muscular dystrophy, and now myelopathic muscular atrophy (of the Aran-Duchenne type and amyotrophic lateral sclerosis) were studied with this method by the authors.

107 points (τ, σ) were individuated in the muscles of the patient's upper limbs; every point was constructed by measuring from 80 to 140 discharge-intervals of single motor unit during voluntary muscle contraction of three different degrees.

There was no significant difference between the two curves K and T formed by the distribution of these points and the curves K and T found by Tokizane in the arm muscles of normal subjects. The curve K (kinetic) particularly is almost identical with the analogous curve of normal men, even as for the extension of its horizontal sector.

The thesis that in myelopathic muscular atrophy the great α-motoneurons with "kinetic" function are damaged preferentially, seems to be denied by this electromyographic investigation.

4. Depressed EEG tracings in infantile encephalitic syndromes. — G. B. Cavaffuti, Modena.

The depression of the EEG potentials in the course of infantile encephalitic syndromes has been observed by us in a number of cases, contrary to what may be found in literature which only exceptionally signalizes remarks of this kind. The circumstances under which the depressed tracing is observed are different, and also the purport of the same, both from the physiopathic and clinical viewpoint, proves variable.

Three electroclinical pictures may be distinguished:

(*a*) encephalitis and encephalotoxic states of the first half-year of life, of variable gravity and prognosis: the tracing remains depressed during the whole continuance of the disease, the elements theta and delta, proper to age, being absent;

(*b*) phase of improvement of encephalitis of different type in the 2nd-5th years of life: in such cases the depression follows a phase of slow dysrhythmia;

(*c*) encephalitis with signs of lesion of the brain stem, often with a decerebration picture: in such cases the tracing is extremely flat, almost coincident with the isoelectric line, and so it may remain even at distance of time, in case of definitive sequelae.

In the first two case the EEG depression seems to document either encephalic incapacity to react to the metabolic suffering or exhaustibility of the reaction, probably in proportion to anatomo-functional immaturity of the brain. In the third case it is suggestive of an involvement of the reticular mesencephalic substance.

5. EEG study of twins. — B. Gatti and L. Gervasio, Milano.

The EEG records in six couples of identical twins ranging from 8 to 20 years of age and suffering from various troubles (5 couples clinically concordant and 1 couple clinically discordant), have been analyzed by the authors.

The normal and pathological characteristics of the background rhythm as well as the degree of bioelectrical evolution were found to be identical in the constituents of each couple of twins.

6. Observations on the action of the enteramine (Serotonine, 5-Hydroxythryptamine) in epileptic patients. Clinical-EEG study. — G. Gomirato and F. Ferro-Milone, Siena.

After a bibliographical review on the 5-HT (enteramine, serotonine), the authors illustrate the effects observed for the administration of 5-HT in 7 epileptic subjects at the lowest dose of 15 mg. intravenously and at the highest of 30 mg., partially intravenously, and partially intramuscularly, for a period of 10 days at least after the discontinuance of anticonvulsive therapy.

Under the clinical point of view, an anticonvulsive action is evident which results at least equal to and sometimes higher than that produced by the usual antiepileptic drugs.

In two cases, the EEG tracing shows evidence of an immediate action (during and soon after the i.v. injection) with reduction of the focal and slow diffuse abnormalities. In a case of "petit mal" epilepsy the reorganization of the basic tracing and the reduction of the frequency of the P.O. *bursts* are so

evident that the authors afford the hypothesis that in the pathogenesis of the ''petit mal'' epilepsy with typical P.O. at 3 c/sec., an altered metabolism of the chemical mediator can be regarded as highly important. In accordance with the literature such a mediator might even be the 5-HT itself or strictly correlated with the 5-HT metabolism. The possibility of an action at the vascular cerebral level is less likely but yet not excluded.

7. Slow and rapid alpha rhythms: statistical comparison; short considerations. — E. Lugaresi and V. Volterra, Bologna.

The authors have put together the cases of those patients hospitalized with alpha rhythms equal to 7 - 8 c/sec. and of those with alpha rhythms equal to 12 - 13 c/sec.

A comparison of the two groups has provided information for discussing the physiopathological and clinical value of brady and tachyrhythmic alpha rhythms.

8. The pathogenesis of flexor spasms in the light of a case in which a nodule of tuberous sclerosis in the head of caudate nucleus was removed. — F. Maccagnani and R. Vizioli, Roma.

The case is described of a child 2 years old, suffering from massive spasms, in which spasms disappeared after removal of a nodule of tuberous sclerosis in the head of caudate nucleus. The nodule was in neoplastic transformation.

The possible pathogenesis of massive spasm is considered also in the light of recent data by Spiegel and coll. on the possible striopallidal substratum of such seizures. Considering the fact that caudate nucleus is one of the most important stations of a central inhibitory system the possibility is considered that in some cases massive spasms are the consequence of a lack of inhibition from caudate nucleus on the facilitating descending reticular system. For what concerns the flexor pattern which is a characteristic of infants and was experimentally produced after destruction of labirinthine nuclei (Davis and Pollock) the possibility is considered that the flexer spasms appear only in infants because of a defective maturation of the labirinthine system. If one bears in mind that in hypsarhythmic children a severe maturation retard is present and/or an anomalous evolution of maturational processes the above hypothesis appears justified. The vestibular system is essential to the maintenance of extensor tonus: its lack of maturation might explain why in infants and only in infants the flexor type of spasms is present.

9. Comparative experiences with intermittent photic stimulation and intermittent sound stimulations in epileptics. — G. Mengoli, Bologna.

Electroencephalographic results obtained by the treatment of 22 epileptic patients with the intermittent photic stimulation and the intermittent sound stimulation are here related. These stimulation methods have been employed separately and simultaneously.

In some cases some correspondence has been found between the reactivity to the photic stimuli and to the acoustic stimuli; although the latter is much rarer and less efficient than the first one. It has been further noticed that the optimal frequency of the respective stimulations was not the same with the same patient and that the photo-acoustic stimulations could induce a change in the optimal frequencies or bring about paradoxal reactions.

Various hypothesis are been elaborated in order to explain obtained results.

10. About an exceptional clinical and electromyographic observation: "Mechanic and active" myotonia, muscular hypotrophia and fasciculations. — L. Ravizza and V. Bergamini, Torino.

A male patient aged 45 had suffered for 4 years from conspicuous hypotrophy of the shoulder and upper arm muscles, of the bicipites of both arms and of the left triceps muscle. In these muscles as well as in the gastrocnemii very frequent fasciculations were present. This picture had remained unvaried for years. By repeated electromyographic checking, six months ago the development of remarkable myotonic phenomena was discovered: showers provoked by insertion of electrodes, by percussion and after voluntary contraction. Other findings were: mean-duration of individual action potentials (55 potentials): 9.6 $\pm$ 0.4 msec.; high percentage (36 per cent) of potentials with a markedly irregular shape; statistic prevalence of triphasic potentials; the study of fluctuation of discharge-interval shows normal K and T curves.

This case represents a picture of atrophia muscularis myelopathica of the Vulpian-Bernhard type; exceptional findings were obvious ''active'' myotonic phenomena (which may be due, very probably, to partial muscular denervation).

11. ACTH in cases of infantile epilepsy (hypsarhythmia not included). — Giovanni Ricci, Roma.

ACTH has been given in a group of epileptic children with EEG and clinical features different from hypsarhythmia (Sorel and col. 1958), whose epileptic seizures were partially or not at all controlled by commun drugs.

The children were given a daily prescription of 5 to 40 i.u. of ACTH (delayed absorbtion) by intramuscular injection during a period from 10 to 15 days.

The previous medical treatment was maintained. In all cases no untoward effects were shown.

The full control of the seizures was obtained 24-72 hours after the beginning of the treatment in cases of akinetic epilepsy (4), petit and grand mal (3) and epileptic status (a 5 month old child).

In all these cases no abnormal features either in neurological and psychological clinical picture were shown. At present, from 6 days up to 2 months after the start of ACTH, they are still well.

Transient or no results at all were observed in 2 cases of akinetic epilepsy with dementia and in 4 cases of epilepsy with serious brain dammage.

The clinical improvement was shown through the EEG: after a transient decrease in frequency and amplitude of the basic activity, and a reduction of the fast rhythms, a decrease and finally a steady disappearance of the epileptic anomalies (from 3 up to 7 days after the beginning of the treatment) was observed.

Although the number of the cases is too little to reach any available conclusion, nevertheless it one may think that ACTH works in centroencephalic epilepsy and that its activity is better where a satisfactory anatomical and functional state of the brain does exist.

12. Studies on myotonic after-spasm. — E. Sala and F. Savoldi, Pavia.

After-spasm was studied in dystrophic myotonic patients following maximal voluntary activity and electrical stimulation of the nerve with tetanizing frequencies. Trials on different positions of the limb allowed to analyze the influence of the proprioceptive impulses under stretching of the antagonistic muscle. Such impulses dont quite explain the whole behavior of the myotonic after-spasm.

13. The value of systemic EEG examinations in professional poisonings and workers diseases. — C. Serra and L. Ambrosio, Napoli.

The results of systemic EEG investigations upon the most frequent professional poisonings (*lead intoxication,* 61 cases; *carbon disulphide intoxication,* 42 cases; *carbon monoxide poisoning,* 20 cases; *DDT poisoning,* 10 cases; and experimentally in rabbits induced CO, CS_2, Benzole, tricloroethylaen, tetraethyllead, mercury and manganese intoxications) and workers diseases (*cassonism disturbances,* 58 cases; *electric traumata,* 30 cases) are exposed.

Very frequent signs of ''trophic'' disturbances were recorded in carbon disulphide, lead, DDT intoxications and cassonism disturbances, with simultaneous biological changes (alteration of serum ionic balance). In lead poisoning ''photic driving'' patterns during I.P.S. were frequently observed.

Depression and desynchronization of electrocortical activity were observed in acute stages of various experimental poisonings (CS_2, benzole, tricloroethylen, CO, manganese and mercury) and human CO-intoxication, with progressive improvement of electric cortical activity simultaneously with clinical improvement.

Regional or diffuse EEG alterations were frequently observed in acute stage of electric traumata, with trend to progressive regression both of clinical and electrical pathologicaI signs.

14. An attempt of interpretation of the memory disturbances following ECT in the light of recent data on physiopathology of memory. — R. Vizioli, G. Cerquetelli, C. Catalano-Nobili and F. Maccagnani, Roma.

Considering the fact that the only disturbance following ECT is a disturbance of memory of short duration a possible explanation of the fact is proposed. Recent data by Penfield and Milner show that hypocampus is a structure where conscious experience is temporarily registered. The hypothesis is advanced that during ECT the electrical discharge has its main effects on hyppocampal structures. This view is supported by the well known lowest convulsive threshold in hyppocampus. If hyppocampus has the lowest convulsive seizure, if hyppocampus plays an important role in temporary registration of conscious experience, it is possible that loss of memory after ECT is due to a prolonged disroder in hyppocampal electrical function set off by the electrical discharge.

15. Electroencephalographic and psychogalvanic variations in the verbo-motor conditioning test. (Research technique and preliminary observations). — G. Zanocco and V. Volterra, Bologna.

After examining the results and considering the uncertainties in the data furnished by electroencephalographic research in the field of psychopathology, the Authors reached the conclusion that in this branch, the use of a more dynamic and complete plan of research would be opportune, a plan embracing, together with electroencephalographic registration, the rate of the peripheral psychovegetative variations and a central nervous process test.

To this end the Authors made use of the electroencephalographic exam and the psychogalvanic reactivity one (according to a technique worded out in preceeding research studies) carried out during verbo-motor conditioning according to Ivanov-Smolenski (illustration of the instrumental apparatus and the method).

The research was carried out on three main groups of subjects-normal, anxious and hysterical-immature, by testing:

(1) base EEG activity and electroencephalographic reactivity;
(2) spontaneous behaviour and psychogalvanic reactivity to elementary stimuli (startle reaction) and word association test;
(3) verbo-motor conditioning capacity and relative EEG and PG behaviour.

The experience gained up to the present has enabled the Authors to notice the EEG and PG variations accompanying the various conditioning phases and some differential aspects regarding learning capacity in relation to EEG and PG activity.

16. Electroencephalographic study of patients affected by depressive state treated with imipramine hidrochloride (iminodibenzyl derivate G 22355-Tofranil). — R. Zappoli, Modena.

Forty-two patients affected by a depressive state, were examined from an EEG point of view. Before treatment with imipramine hidrochloride was begun, 31 patients had a normal EEG, while 11 (mostly hypertensive and old-aged) had diffuse alterations of the records, aspecific and not very accentuated. Administration of high doses of the drug (300-350-400 mg/ 24 h.) caused more or less important modifications of cortical biorhythms in 18 subjects (43 per cent). These EEG modifications may be classified as follows:

(1) tendency to desynchronization with reduction of occipital alpha rhythm; accentuation of beta rhythm in anterior and central regions (7 cases);

(2) accentuation of pre-existing alterations (6 cases);

(3) appearance of diffuse cerebral hyperexcitability EEG patterns, with irritative notes: rapid rhythm and accentuated theta dysrhythmia prevalent in the anterior and central leads, with irregular waves mixed with numerous sharp elements having the aspect of slow spikes; sometimes tendency to hypersynchronism phenomena with brief generalized discharges of slow waves and sharp waves (10 cases);

(4) appearance of an epileptic dysrhythmia: brief, generalized discharges of wide, slow, hypersynchronous waves and of slow spikes, variously combined, sometimes with an aspect of irregular spike-wave complexes (4 cases);

(5) accentuation of the dysrhythmia and slowing down of the cortical bio-rhythms with facilitation of hypersynchronism phenomena on overbreathing (10 cases).

In several subjects mixed findings were observed: i.e. more than one of the above mentioned EEG modifications were present. The meaning of these EEG findings are discussed and some hypotheses on the probable mode of action of this substance are put forward.

THE SWEDISH CLINICAL NEUROPHYSIOLOGICAL SOCIETY

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May 23, 1959

1. Observations on the neurophysiological mechanism of trigeminal neuralgia. — E. KUGELBERG and U. LINDBLOM, Stockholm.

2. Hypothyroid myopathy. — E. KUGELBERG, R. MÜLLER and K.-E. ASTRÖM, Stockholm.

The skeletal muscles have been studied in four patients with spontaneous myxoedema and one patient with artificially produced hypothyroidism.

In one case there was weakness, hypertrophy and a tough consistence of the extensor muscles in the lower legs. Three cases had pareses especially proximally in the lower legs. The fifth patient had normal strength. There were no atrophies, fasciculations or myotonic reactions. The Achilles tendon reflex was tonic in three cases. Otherwise the reflexes were normal.

There was no correlation between the degree and duration of the thyroid insufficiency and the muscle symptoms.

Electromyography revealed in all cases spotty changes which were most pronounced in the proximal muscles of the extremities and indicated a primary myopathy, *i.e.* the action potentials were of short duration and often polycyclic. There was no spontaneous or insertion activity.

Biopsies demonstrated in all cases alterations in single or groups of fibers such as swelling, hyalinization, granular and vacuolar degeneration and invasion of inflammatory cells into the necrotized areas. There were only slight tendencies to regeneration. Fibrous tissue and fat replaced the destroyed fibers and enclosed their remnants. The histologic findings suggest a primary degenerative affection of the skeletal muscles ensued by normal reparative processes.

3. Neurological diagnosis of level of lumbosacral root compression. — L. HERLIN, Stockholm.

4. Measurements of oxygen and carbon dioxide tension on the surface of the cerebral cortex. — D. H. INGVAR and B. SIESJÖ, Gothenburg.

In unanaesthetized and anaesthetized cats electrodes were applied to the exposed intact pial surface of the cerebral cortex for measurements of local oxygen and carbon dioxide tensions. The oxygen electrode consisted of a multiple platinum wire polarographic device covered by a polyethylene membrane (Lübbers and Ockenga 1958). For carbon dioxide tension measurements a new type of electrode was employed (Hertz and Siesjö, 1959). Both electrodes proved to yield stable and reproducible results and they reacted fast to rapid induced changes in tissue pO_2 and pCO_2. Changes in the functional cortical activity (as measured by the EEG) brought about by electrical stimulation of the brain stem (arousal reactions) or by administration of Metrazol (epileptic seizures) resulted in an initial diminution of the cortical surface pO_2 and an increase of the pCO_2 value recorded. Similarly, a diminution of the cortical metabolism by, e.g. barbiturates or potassium cyanide, gave opposite effects. The relationship between arterial tension of oxygen and carbon dioxide on the one hand and respective cortical surface tensions on the other, was studied especially. Some preliminary conclusions as to regulatory mechanisms could thus be reached.

ANNOUNCING A NEW EEG SOCIETY

Sociedad Mexicana de Electroencefalografía

The Mexican Society of Electroencephalography was formed in July 1959. The officers are as follows:

President: J. Hernández Peniche
Secretary: C. Gunther Strecker
Treasurer: P. Ortíz Estrada

On behalf of the International Federation and the EEG Journal we take pleasure in congratulating our Mexican colleagues and extend to them our sincere best wishes.

PRINTED IN CANADA

BOOK REVIEWS

Edited by CHARLES E. HENRY

THE SHERRINGTON LECTURES

IV. SHERRINGTON : PHYSIOLOGIST, PHILOSOPHER AND POET

LORD COHEN OF BIRKENHEAD

Charles C. Thomas, Springfield, Illinois, 1958, 108 pp., $3.50

Sherrington: Physiologist, Philosopher and Poet, by Lord Cohen of Birkenhead, is an admirable portrait of one of the greatest scholars in this era of scientific production. The first lecture tells the story of his life and his many friendships. In this chapter the rare modesty of the man is shown, and the courteous deference to the opinions of others. The story about seeing ''eye-to-eye'' with the chimpanzee through the keyhole, was probably modified in the later telling, for Nisbett, the electrician, told me he was the one who met the ape's eye looking into his through the keyhole.

Lecture II presents a clear picture of Sherrington's achievements as a physiologist. With considerable detail the account shows how profoundly Sherrington influenced the course of neurophysiology and through this the whole field of clinical neurology. The reader will see in Sherrington an eager and astute observer, a patient and meticulous experimenter, and a profound thinker, elucidating the deeper meanings of his observations on reflex action and cerebral activity, as they led to the integration upon which our lives as sentient and constructive beings depend. Rarely, indeed, has any man lived to see his scientific achievements bear such rich fruit in intellectual progress and benefit to mankind.

Lecture III tells of Sherrington: Philosopher and Poet. Throughout his life he was a philosopher as well as a scientist; but after his retirement in 1935 he found more time to study and meditate on the philosophical implications of science and especially of neurophysiology. In ''Man on his Nature'' (the Gifford Lectures) Sherrington showed much preoccupation concerning the age-old problem of the relation of mind to body. Lord Cohen quotes a number of passages from this work. In these Sherrington frankly stated that to him the relation of mind to the material body was still an enigma. Stressing the basic difference between subjective experience and objective findings, he insisted that dualism must be recognized and accepted.

There can be no doubt that all anyone knows directly is the content of his own consciousness; even the readings of physical events, which the scientist writes in his note-book, are taken from his conscious experience imparted by his senses. A man may feel reasonably and justifiably sure that he has insight into the conscious experience of a sympathetic friend with whom he communicates freely, but all he really knows directly is what goes on in his own consciousness.

To the reviewer it seems that this subjective-objective dilemma is resolved, as far as it can be, in the conclusion of Lloyd Morgan (''Introduction to Comparative Psychology'' pp. xiv and 382): ''Monism regards nature and experience as one and indivisible, and all apparent dualism, as a dualism of aspect, distinguishable in thought, but indissoluble in existence.'' To a man inside a hollow sphere the surface is concave; to the observer outside it is convex, but despite the difference in aspect, it is one and the same surface. The subjective and objective aspects of brain function are somewhat similarly related.

In conclusion Lord Cohen discusses Sherrington as a poet, noting that his deepest emotions found expression in his poems. While recognizing that in many of Sherrington's poems the wording is involved and sometimes hard to follow, he pays warm tribute to the beauty and sincerity of the finest works of Sherrington as a poet.

ALEXANDER FORBES

PRINTED IN CANADA

BASES PHYSIOLOGIQUES ET ASPECTS CLINIQUES DE L'ÉPILEPSIE

TH. ALAJOUANINE (Ed.)

Masson et Cie, Paris, 1958, 273 pp. 2.300 frs

This book contains the lectures given at the 1957 ''Semaine Neurophysiologique de la Salpetrière''. The meeting was devoted to the very broad subject of the physiological basis and clinical and electroencephalographic aspects of epilepsy. Professor Th. Alajouanine himself explains in his introductory speech that the purpose of this reunion is not to make a complete survey of the field, but to give the opportunity to different physiologists, clinicians or electroencephalographers to define our present knowledge concerning some of the essential questions.

Prof. F. Bremer, from Brussels, discusses the problems of excitation and inhibition of the epileptic phenomena. He brings to mind the possibility of creating an epileptic focus either by direct electrical excitation or iterative stimulation or strychnine and studies the mechanisms of invasion and generalization to conclude by considerations on the axonic discharge of the nerve cell in a convulsive state and the factors of slowing down and stopping this convulsive activity.

Prof. A. Fessard, from the ''Collège de France'', presents another aspect of the physiological basis of epilepsy in analysing the mechanisms of interneural synchronization differentiating the external and internal synchronizations. He reviews the anatomical and dynamic factors of synchronization and discusses the role of the synaptic connections and of the purely electrical interactions.

Prof. G. Morin, from Marseille, devotes his contribution to some vegetative manifestations during experimental epilepsy, showing the characters of the hypertension due to the epileptic seizure and evaluating the influence of this ''epileptic hypertension'' on the seizure itself. He then discusses the role of adrenaline.

Mr. Grey Walter from Bristol, England, brings new notions about epilepsy from his work on low voltage signals. He studies the effect of visual stimulation on normal and epileptic subjects with his toposcope, and interpretes the results with a cybernetic approach. He invites one to consider the brain as a learning filter working on a statistical basis.

Prof. Th. Alajouanine and his collaborators from the Salpetrière, Prof. P. Castaigne, Dr. A. Buge and Dr. R. Lecastle present electroclinical correlations in 100 cases of non-tumoral epilepsies. The careful selection of the cases studied by the same medical team with the same methods permits the authors to discuss the relative value of clinical, electroencephalographic and other paraclinical approaches to establish a final diagnosis. They compare their statistics to those of Grey Walter and Penfield and Jasper.

Dr. W. Penfield, from Montreal, who was chairman of the meeting, gives in his paper a study of temporal seizures in view of the localization of certain psychic functions differentiating experiential, interpretative and amnesic and automatic seizures.

Porf. H. Gastaut, from Marseille, speaks about the clinical symptoms found among the psychomotor epileptics between their seizures. He gives a precise and extensive classification of those somatic, vegetative and psychic intercritic symptoms and then discusses their physiopathological interpretation. He concludes that the psychomotor epileptics present between their seizures a permanent and progressive state of irritation of their para-rhinal structures, this state being responsible for the intercritic and precritic symptoms. During the seizures themselves a paroxystic rhinencephalic discharge is responsible for the critical symptoms themselves.

In a second paper about the neuronal discharges occurring at a distance of an epileptogenic lesion Prof. Gastaut studies the occipital discharges and the visual seizures which accompany the lesions of the so-called ''temporal epilepsy''. He presents 10 electro-clinical observations in which the occipital paroxystic activity responsible for a visual seizure are related seven (7) times to an epileptogenic para-rhinal lesion.

Dr. R. Lecasble publishes a survey about the myoclonic epilepsies opposing the myoclonies of partial epilepsies (Kojevnikoff) to the myoclonies of generalized epilepsies (with the progressive myoclonic epilepsy of Unverricht and the Generalized Epilepsy with intermittent and sporadic myoclonies).

Prof. Alajouanine and Prof. Gastaut's presentation on the startle syncinisia and startle epilepsy gives them the opportunity to observe 30 cases of the newly individualized startle epilepsy which they compare to the cases of startle syncinisias previously reported by Alajouanine and Sherrer. It gives them also the occasion to discuss the nosologic classification of the reflex epilepsies in function of the hypotonic, atonic or hypertonic components during the seizures.

Prof. G. Heuyer with his collaborators of the Clinic of Infantile Psychiatry of the Salpetrière comments about the notion of evolutivity in infantile epilepsy.

The interest of this contribution is based on the large number of cases studies which permits the authors to precise certain prognosis criteria.

Dr. B. C. Ledeboer, from The Netherlands, concludes the meeting with medico-social considerations about epileptics and suggests very practical remedies which coincide with the program of the International League against Epilepsy, of which Dr. B. Ch. Ledeboer has been the devoted president for a long time.

M. DONDEY

ELECTRONIC APPARATUS FOR BIOLOGICAL RESEARCH

P. E. K. DONALDSON

Butterworth, London and Toronto; Academic Press, New York, 1958, , pp. 120 s. $20.00

Without doubt this is the most comprehensive and useful book on biological electronics which has appeared to date. The author has planned well and both his choice of subject matter and its arrangement are excellent. The book is divided into four parts: Theory; Practice; Transducers, Electrodes and Indicators; and Complete Apparatus. The first section is an extremely happy compromise between qualitative circuit description and a formal mathematical treatment. It is excellently suited as a basis for postgraduate courses in medical electronics and will probably become the standard textbook for students in this field.

The high standard which the author has set himself invites criticism of some details; this is offered not in any spirit of churlishness but in the belief that the utility of the work could be greatly extended, especially to American students, by a certain amount of revision and modification. The book is, after all, an expensive work — it is the highest priced textbook in current use in this Medical School — and the student is entitled to a corresponding return on his investment. It would be fairly easy to extend the references to include works more readily available to the American biologist. In any case many more references should be cited and if the reviewer may be permitted to venture on to somewhat precarious ground he would like to question some of the sources which the author quotes as original.

Inevitably the section on ''Practice'' relates primarily to British practice and the worker outside the United Kingdom will gain little from this part of the book. The author can scarcely be blamed for writing within his experience but in a number of instances he has thoughtlessly restrictedt he value of his work. For example on page 320 there is a very sensible list of valves (vacuum tubes) showing their salient characteristics. Nearly lal these are available in the United States with different designations; cross reference to American types would have involved only trivial additional effort. The author's normally precise use of units is not extended to the half-tone illustrations of various electronic components. Much use is made of the ''Matchbox'' as a unit of length; if Dr. Donaldson is very enthusiastic about this unit he should include a conversion factor since one Imperial matchbox is approximately equivalent to 0.45 U.S. matchbox.

Probably the most valuable section of the book to the practicing biological worker is the section on transducers, electrodes and indicators, although this reviewer is inclined to quibble at the title since he would include electrode systems under the general heading of transducers. In this section the author has called on the specialist services of his colleagues to produce an extremely authoritative and complete set of essays on the manifold problems of coupling biological preparations to electronic instruments. This section should be read and understood by all who have an interest either in the design of equipment or in the interpretation of data.

In summary the work is a creditable addition to the long list of achievements of the Cambridge school of Physiologists. Sir Bryan Matthews, in his foreword to the present book, points out that Cambridge research students must demonstrate their ability to construct and understand rudimentary apparatus. The clear, concise and common sense approach to instrumentation which Donaldson and his co-workers display is evidence of the value of this discipline and an example which, if followed, would be of immeasurable value both to the individual student and the general field of the biological sciences.

H. W. SHIPTON

PRINTED IN CANADA

CONTRIBUICAO AO ESTUDO CLINICO DA EPILEPSIA TEMPORAL

Manifestacoes clinicas em 1000 pacientes portadores de foco temporal no electroencefalograma

JORGE ARMBRUST FUIGUEREDO
São Paulo, Brasil, 1958, 285 pp.

This monograph is a valuable contribution to the clinical knowledge of temporal lobe epilepsy. Though there is nothing essentially new in it, the unusually large number of cases examined, and the statistical evaluation of every single clinical manifestation, makes this an interesting piece of work.

Out of case material of 16,421 patients suffering from all types of epilepsy, from the Neurology Department of the School of Medicine of São Paulo, Brasil, the author selected 5,214 (32 per cent) which showed localized electroencephalographic temporal disrhythmia, the purpose of the author being to investigate the possibilities of establishing the clinical symptomatology of temporal lobe. He eliminated out of these 5,214 all cases showing gross lesions that might or did extend to other neighbouring areas of the brain, like infantile encephalopathy, intracranial tumours, obvious cerebrovascular disease, etc., etc. All cases not showing normal cerebro spinal fluid were also discarded, as well as children younger than ten years of age, because of the difficulty of obtaining an accurate clinical picture, mainly of the subjective manifestations. There remained 1042 cases, but only 1000 cases were considered to facilitate the statistical calculations.

In the first chapter the author gives a concise summary of the anatomy and physiology of the temporal lobe. The second chapter is devoted to the study of the concept of psychomotor and temporal epilepsy as well as the pathology of the temporal lobe epilepsy, following the historical development of the research since Jackson to the present time. In chapter III the material and method for his study are presented. The criteria for the selection of cases was the presence of cortical or subcortical electroencephalographic foci with strictly temporal projections limited to the lobe, as described by Jasper and coll. Records were registered following the technique of the Montreal Neurological Institute. The chapter ends with one section devoted to the definition of the clinical manifestations. In chapter IV the author proceeds to the description and statistical evaluation of every clinical manifestation of his cases. These he divides in (*a*) paroxistic and (*b*) interparoxistic or permanent. Each of these two groups in turn are sub-divided in (1) subjective and (2) objective manifestations. On the whole he finds paroxistic disturbances of consciousness in 93 per cent of the cases, automatisms in 63 per cent; objective, psychological manifestations in 62 per cent, subjective psychological ones in 58 per cent. Sensorial subjective, mostly visual, auditory and vestibular symptoms are found in 48 per cent. Vegetative, subjective (mostly digestive and vascular) manifestations are seen in 45 per cent. Among permanent interparoxistic symptoms 35 per cent were objective and 28 per cent subjective in nature.

Only 13 per cent of the cases showed bilateral electrographic projections. In this group there was a higher frequency of generalized seizures and fugues and of mental and emotional symptoms both paroxistic and permanent. Among the cases showing unilateral projections a slight predominance of the left temporal lobe over the right is observed. The changes were localized in the anterior pole, in 84 per cent of cases.

In chapter VI the author discusses every symptom shown in his case material in connection with the findings of the other investigators. This chapter seems, for the reviewer, the most useful of the monograph, and should be consulted for the reader interested, since it cannot be summarized. Finally the author concludes that the multiplicity of clinical manifestations observed in his case material all coincides with the symptomatology of the temporal lobe as described in the literature of clinical and experimental observations in man. The relative uniformity of the symptoms, paroxistic as well as interparoxistic, and particularly the great frequency with which some of them are found, seem sufficient, according to him, to establish the existence of a defined clinical syndrome which makes possible the diagnosis of a localized temporal lobe epilepsy.

The monograph ends with a bibliography complete with 393 references.

This excellent clinical study would have been more convincing should the author have considered the necessity to substantiate his clinical findings with more objective EEG evidences. In spite of the subtitle, no one single electroencephalographic record appears in the publication. Unfortunately the fact that this monograph is written in Portuguese considerably restricts the number of readers who could benefit from the many useful clinical and statistical data that only reading in the original can be appreciated.

MIGUEL PRADOS

ÉPILEPSIE

Étude Clinique, Diagnostique, Physiopathogénique et Thérapeutique

J. A. CHAVANY

with preface by Professor PETIT-DUTAILLIS and a chapter on
electroencephalography by G. LOBEL and a chapter on medico-social problems by D. HAGENMULLER

Masson et Cie, Paris, 1958. 356 pp., 24 fig. 2.800 fr.

This book gives a description of epilepsy which is adequate for a first reader in this subject. It covers all the important aspects of the subject. It adds no new material. It first discusses in seven pages generalized seizures; that is, grand mal and petit mal which it divides into ''absence'', myoclonic and inhibitory (akinetic). This is followed by an account of partial seizures; that is, jacksonian, motor and sensory seizures, sensory and ''psychosensory'' seizures, special alterations of consciousness, adversive seizures, psychomotor automatisms, aphasic seizures, viscerovegetative seizures, ''hyper- and hypotonic'' seizures and a ''synthesis of partial seizures'' on the anatomic basis of the five lobes of the brain. Subcortical origins are not mentioned.

In the second part ''special aspects'' are discussed such as, acute mental disorders, dementia, delirium, and suicide; nocturnal epilepsy, ''epileptic myoclonus'' and ''myoclonic epilepsy'', epilepsy in early and late infancy, idiopathic epilepsy beginning after twenty-five years of age, reflex epilepsy, epilepsy and heredity and ''epileptic predisposition''.

The chapter on electroencephalography is written by G. Lobel of Brest. It is forty pages long, has twenty-two figures, and a bibliography of eleven ''principal works consulted''. The author considers in elementary terms: the normal electroencephalogram, the abnormal electroencephalogram, the seizure and between seizure electroencephalogram in grand mal, petit mal, superficial and deep temporal lobe epilepsy, diencephalic psychomotor epilepsy, focal epilepsy, methods of activation, and sources of error. The author gives no statement of his personal experience and no figures concerning the relative occurrence of normal and abnormal patterns. In brief, this is an elementary account of electroencephalography as it applies to the study of epilepsy. This is followed by chapters on differential diagnosis and a discussion of common etiologic agents.

The fourth part discusses physiopathology; that is, the propagation of the discharge, extinction, etc., metabolic and endocrine factors. Both medical and surgical types of treatment are discussed.

The final part of the book is a discussion of ''medico-social problems posed by epilepsy'' written by D. Hagenmuller.

Although the reviewer does not approve of the classification of types of seizure, the book is considered a good, complete but elementary introductory text on epilepsy for French reading medical students.

D. J. SIMONS

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MASKED EPILEPSY

HUGH R. E. WALLIS

E. & S. Livingstone Ltd., London, 1956, 51 pp. $1.20

Dr. Wallis draws our attention to the fact that a number of symptoms commonly found in children such as abdominal pain, cyclic vomiting and paroxysmal headache may be of organic cerebral origin. He presents illustrative case histories of a kind that will be very familiar to paediatricians and points out that if the cerebral origin of the symptoms is recognized much unnecessary investigation and even surgical procedures may be avoided. Although this important concept has been recognized for some considerable time, surprisingly little has been written about it and Dr. Wallis' contribution is timely in this regard.

His use of the term ''masked epilepsy'' is open to criticism. Epilepsy is defined in the Oxford dictionary as being ''characterised by paroxysms in which the patient falls to the ground unconscious with general spasms of the muscles, foaming at the mouth''. Whilst few neurologists would care to delineate epilepsy as precisely as this it is usual to restrict its use to those conditions in which a generalized seizure is likely to occur in the natural history of the disease process. The symptom complexes described by Dr. Wallis, whilst undoubtedly being of organic cerebral origin, are rarely complicated by major seizures and, in the majority of cases, disappear in adult life without treatment. To call them epilepsy — any kind of epilepsy — may lead to confusion in the profession and anxiety in the family.

The main evidence for the ''epileptic'' nature of the symptoms is based on the electroencephalographic findings and the response to medication. They are both, as presented, untenable. The correlation between electroencephalographic patterns and clinical entities is empirical at best and their interpretation, unfortunately, varies rather widely from person to person. To be generally meaningful the wave forms must be described objectively which Dr. Wallis has not done. Dr. Wallis points out that many of the symptoms disappear or are considerably improved when small, continuous doses of phenobarbitone are given. Most people would disagree however with his statement that because a symptom is improved or disappears on treatment with phenobarbitone it is epilepsy.

The book contains an idea that is important and should be widely recognized. It is a pity that it is not better documented.

JOHN STOBO PRICHARD

ERRATA

In the August issue, page 448, figure 3 was printed backwards and upside down.

Dr. Klapetek's and Dr. Veit's *et al.* articles, published in this issue, page 809, were included, by mistake, in the Table of Contents for the August issue.

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